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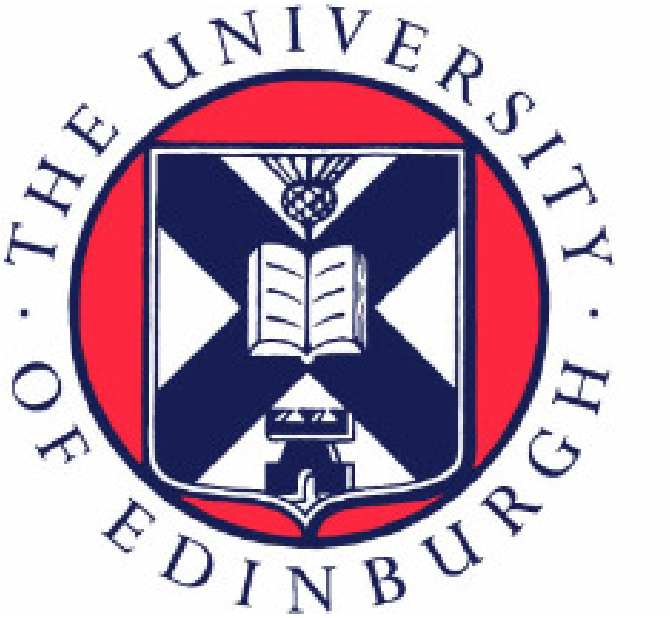

The Development of New Methodology for the Synthesis of Fluorine-Containing Compounds

Thesis Submitted in Accordance with the Requirement of the University of Edinburgh for the Degree of Doctor of Philosophy

By

Samantha Brogan

MA/MSci

PhD – University of Edinburgh - 2012

Declaration

I hereby declare that, except where reference is made to other sources, the work contained within this thesis is the original work of my own research since registration for the PhD degree in September 2008 and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or in part, for any other degree, diploma or other qualification.

Signed

Samantha Brogan

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First of all, I would like to thank my supervisor Dr Hon Wai Lam for giving me the opportunity to work in the Lam group and providing support, facilities and ideas throughout my PhD studies.

I would also like to thank my industry supervisor Dr Neil Carter for all the assistance given during my PhD and particularly during my placement at Syngenta. Thanks also go to Syngenta for the provision of funding.

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thesis in their own right, so I also give my thanks to Serghei, Alain, Martin, Darryl, Bonnie, Alison, Boris, Jen (an honorary Lam group member), Suresh, Yunfei, Sit and Johnathon.

Last but not least, this thesis is dedicated to my family: mum and dad, Anthony and my grandparents, for all of their help (including financial!) throughout the many years of studying that have brought me to this point.

Contents

List of Abbreviations

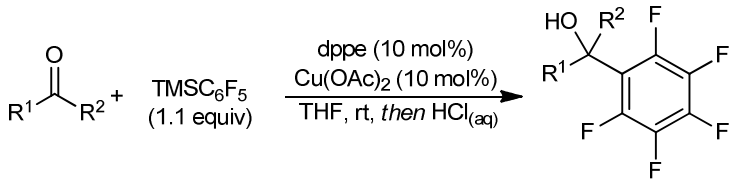
Ac	acetyl
acac	acetylacetonate
app	apparent
ASAP	Atmospheric Solids Analysis Probe
BDPP	2,6-Bis-(2,6-diisopropylanilidomethyl) pyridine
BINAL	Binaphthol
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
BPE	Bis(dimethylphospholano)ethane
br	broad
CI	Chemical Ionisation
cod	cyclooctadiene
coe	cyclooctene
d	doublet
dba	dibenzylideneacetone
DBU	1,8-Diazabicycloundec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
de	diastereomeric excess
DEMS	Diethoxymethylsilane
DEPT	Distortionless Enhancement by Polarisation Transfer
DMAP	Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
dppb	diphenylphosphinobenzene
dppe	diphenylphosphinoethane
dppf	diphenylphosphinoferrocene
dr	diastereomeric ratio
ED_{50}	Median effective dose
ee	enantiomeric excess

EI	Electron Impact
ent	enantiomer of
ES	Electrospray Ionisation
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
HPLC	High Performance Liquid Chromatography
HOESY	Heteronuclear Correlation Spectroscopy
HRMS	High Resolution Mass Spectroscopy
IC_{50}	Half maximal inhibitory concentration
IR	Infra-red
LA	Lewis acid
LDA	Lithium diisopropylamide
m.p.	Melting Point
MS	Molecular Sieves
Ms	Mesyl
MTBE	Methyl *tert*-butyl Ether
Nbd	norbornadiene
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
Nu	Nucelophile
PMHS	Polymethylhydrosiloxane
ppm	parts per million
psi	pounds per square inch
q	quartet
R_f	Retention factor
rt	room temperature
SCX	Strong Cation Exchange
s	singlet
sept	septet
t	triplet
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetrabutylammonium fluoride
TBAT	Tetrabutylammonium triphenyldifluorosilicate
TCFP	Trichickenfootphos

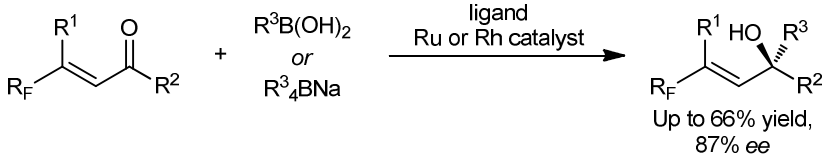
tert	tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMAF	Tetramethylammonium fluoride
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl
UV	Ultraviolet

Abstract

A set of mild conditions for the pentafluorophenylation of carbonyl compounds employing copper-bisphosphine catalysis have been developed. The optimised conditions allow access to a wide range of pentafluorophenyl benzyl alcohols in high yields. The reaction of aliphatic aldehydes and particularly electrophilic ketones to give products in moderate yields is also disclosed.

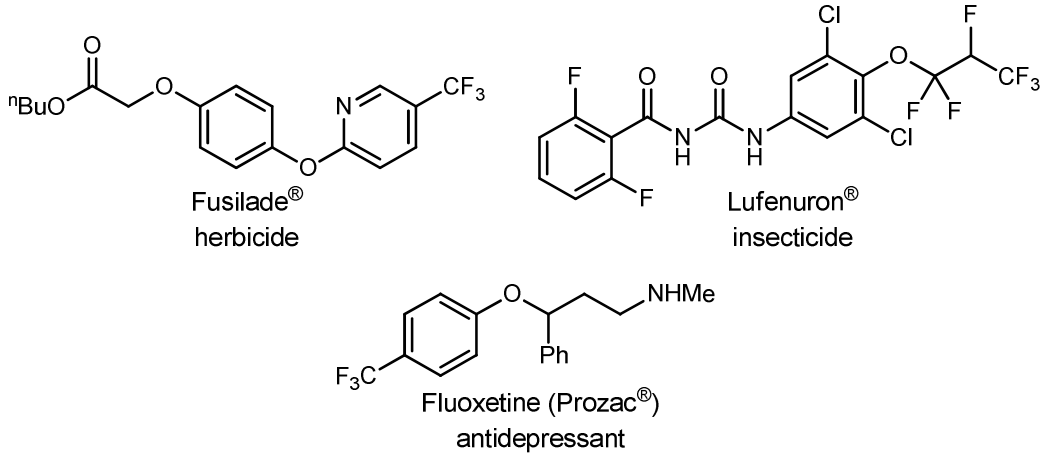


An investigation into the reactivity of *β*-fluoroalkyl-*α*,*β*-unsaturated carbonyl compounds was conducted. Asymmetric copper hydride reduction of *β*-fluoroalkyl-α,*β*-unsaturated ketones was found to preferentially give the allylic alcohol product resulting from 1,2 attack in up to 62% *ee*. Reaction of *β*-fluoroalkyl-*α*,*β*-unsaturated esters under similar conditions gave the product of conjugate reduction in higher enantiomeric excess; up to 99% was observed. Rhodium-catalysed arylation of *β*-fluoroalkyl-*α*,*β*-unsaturated ketones was also found to give the product of direct carbonyl attack. Conditions for the racemic reaction are described along with those for the enantioselective reaction of methyl ketones in up to 74% *ee*. Ruthenium catalysed arylation of *β*-fluoroalkyl-*α*,*β*-unsaturated aldehydes employing Me-Bipam as ligand gave the desired secondary allylic alcohols in good yields and good to excellent enantiomeric excesses (14 examples, 76-87% *ee*).



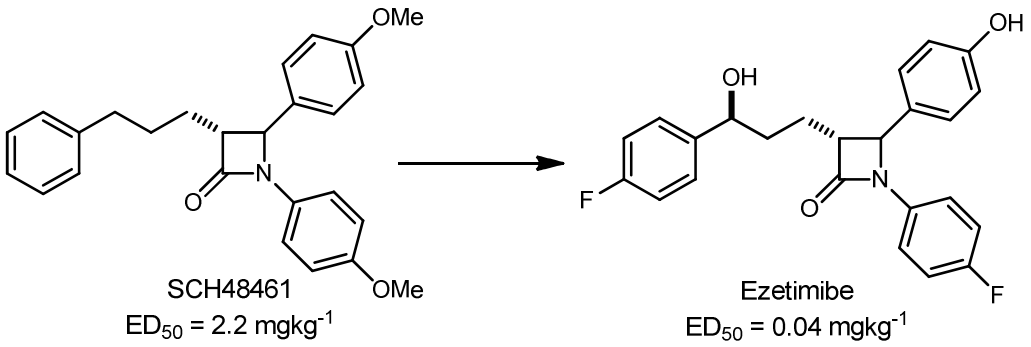
1. Introduction

The incorporation of fluorine into an organic molecule often has a profound effect on its chemical, physical and biological properties.[1] It has been estimated that 30-40% of agrochemicals and 20% of pharmaceuticals currently on the market contain fluorine. Examples are given in **Scheme 1.1**.



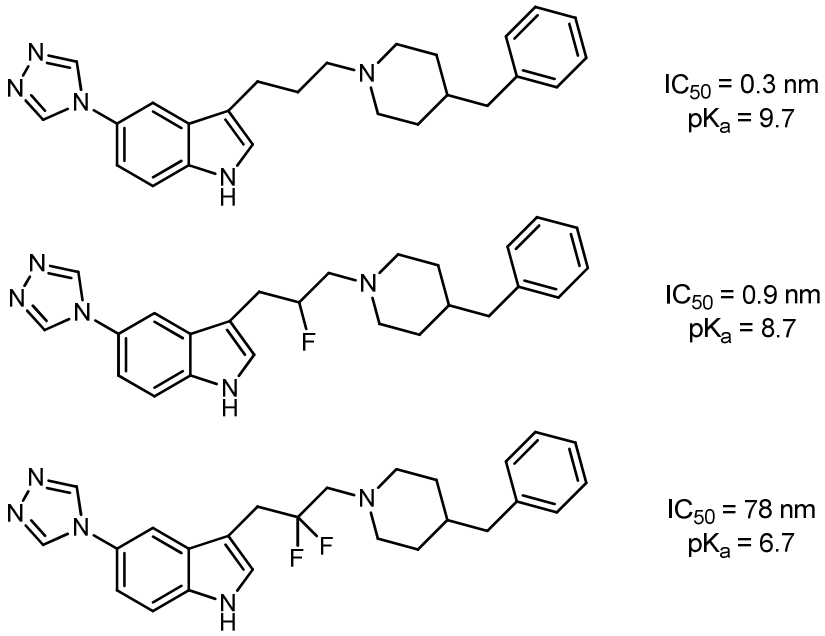
Scheme 1.1

Fluorine is a small atom with a very high electronegativity and it is this combination of properties which means that the introduction of fluorine atoms into commercial compounds is often highly advantageous.[2] There are three common reasons for introducing fluorine into a compound of interest. Firstly, fluorine can increase the bioavailability of a drug molecule by blocking metabolically labile sites, thus preventing oxidation by liver enzymes such as cytochrome P450. An example of this application is Ezetimibe.[3] SCH48461 is a moderately potent compound with an ED_{50} of 2.2 $mgkg^{-1}$ (**Scheme 1.2**). During the development of Ezetimibe, two fluorine atoms were introduced into SCH48461 in order to prevent oxidation of the aromatic rings. This contributed greatly towards the much improved potency of the drug molecule (ED_{50} of 0.04 $mgkg^{-1}$).



Scheme 1.2

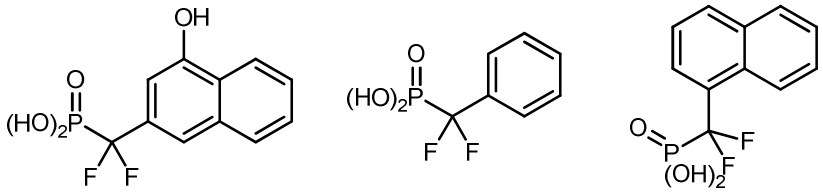
Fluorine (as such an electronegative element) can also be used to increase the bioavailability of a drug molecule by decreasing the basicity and thus increasing membrane permeability. This is illustrated by work carried out on selective $5HT_{1D}$ receptor ligands (**Scheme 1.3**).[4] The introduction of a single fluorine atom into the starting compound led to a decrease in pK_a from 9.7 to 8.7 with a significant increase in bioavailability being observed, along with a small decrease in potency. The difluorinated analogue was also synthesised and had a pK_a of 6.7, however the binding affinity showed a large decrease.



Scheme 1.3

Fluorine substituents can also increase the binding affinity of a compound by strengthening other interactions through a change in the molecular conformation,[5] or by interacting with a

protein itself.[6] Fluorine can have a strong effect on molecular conformations due to the low energy of the $\sigma^*_{C\text{-}F}$ antibonding orbital (itself a consequence of the highly polarised nature of the bond) which leads to its ready participation in hyperconjugation. As a result, fluorine displays an anomeric effect and a gauche effect. Whilst fluorine is generally believed to form only weak hydrogen bonds,[7] both dipole-dipole and charge-dipole interactions have been described. The protein tyrosine kinase 1B inhibitors shown in **Scheme 1.4** are only effective when the fluorine atoms are present. Evidence from X-ray crystallography and kinetic studies suggests that this is due to direct interactions between the fluorine atoms and the active site of the tyrosine kinase.



Scheme 1.4

Naturally occurring fluorine-containing compounds are extremely rare.[8] As a result, organofluorines are almost always accessed by organic synthesis (although enzymes that can perform transformations upon fluorinated compounds have also been discovered[9]). Despite the need for procedures for the synthesis of fluorinated compounds, methodology for the introduction of fluorine-containing functional groups into molecules is currently surprisingly limited. Hence, the most common strategy to access organofluorines is through the functionalisation of commercially available fluorinated building blocks. However, this approach is itself limited by the types of fluorinated building blocks available.

New methods for the introduction of fluorine-containing functional groups in a mild, selective and preferably catalytic manner are, therefore, highly desirable.

2. Copper-Bisphosphine-Initiated Pentafluorophenylation of Aldehydes and Ketones

2.1 Introduction

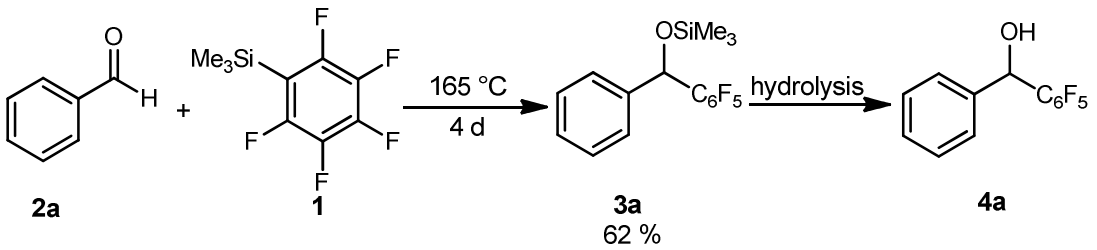
Pentafluorophenyl compounds are of utility in medicinal chemistry,[10] electron-transport devices,[11] light-emitting diodes,[12] printing,[13,14] liquid crystal displays[15] and fluorous biphasic ligands.[16]

In principle, a simple approach for the introduction of pentafluorophenyl groups is the addition of a nucleophilic pentafluorophenyl synthon to an aldehyde or ketone, and this strategy has been accomplished by the use of pentafluorophenyllithium[17] or the Grignard reagent.[18] The yields for these processes are variable, but are generally rather poor. Another drawback is their incompatibility with sensitive functionality.

The successful application of trifluoromethyl(trimethylsilane) to the trifluoromethylation of a range of functionalities has led to a recent increase in the use of silicon-based reagents for the introduction of other fluorine-containing functional groups.[19] Advantages of such reagents are their stability, non-toxicity and relatively low cost. Fluoroalkyl silanes do not themselves react with electrophiles at an appreciable rate. However, the silicon centre is highly susceptible to nucleophilic attack, giving rise to a pentavalent silicon complex, which can transfer the fluoroalkyl group to a suitable electrophile.

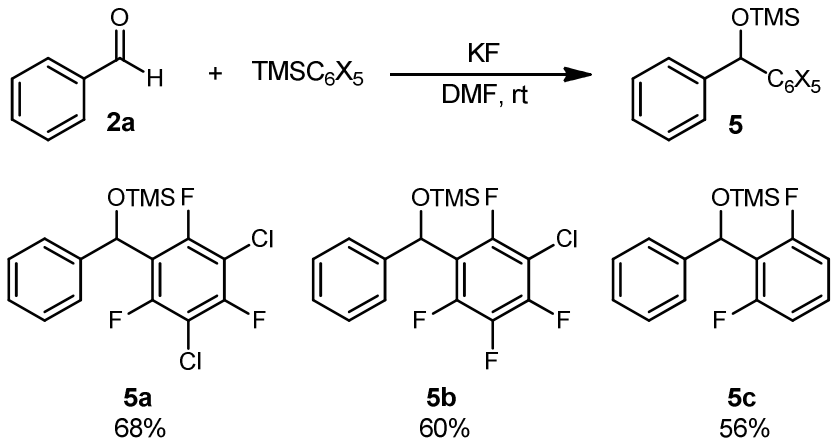
2.1.1 Pentafluorophenylation with (Pentafluorophenyl)trimethylsilane

The first report of a pentafluorophenylation reaction utilising (pentafluorophenyl)trimethylsilane (**1**) was by Gilman and co-workers in 1970.[20] They reported that **1** reacted with benzaldehyde (**2a**) to form the desired pentafluorophenyl alcohol derivative after heating the two together at 165 °C for 4 days and hydrolysing the resulting trimethylsiloxy derivative (**Equation 2.1**). Although the obtained yield of 62% is encouraging, the high temperature and long reaction time are undesirable.



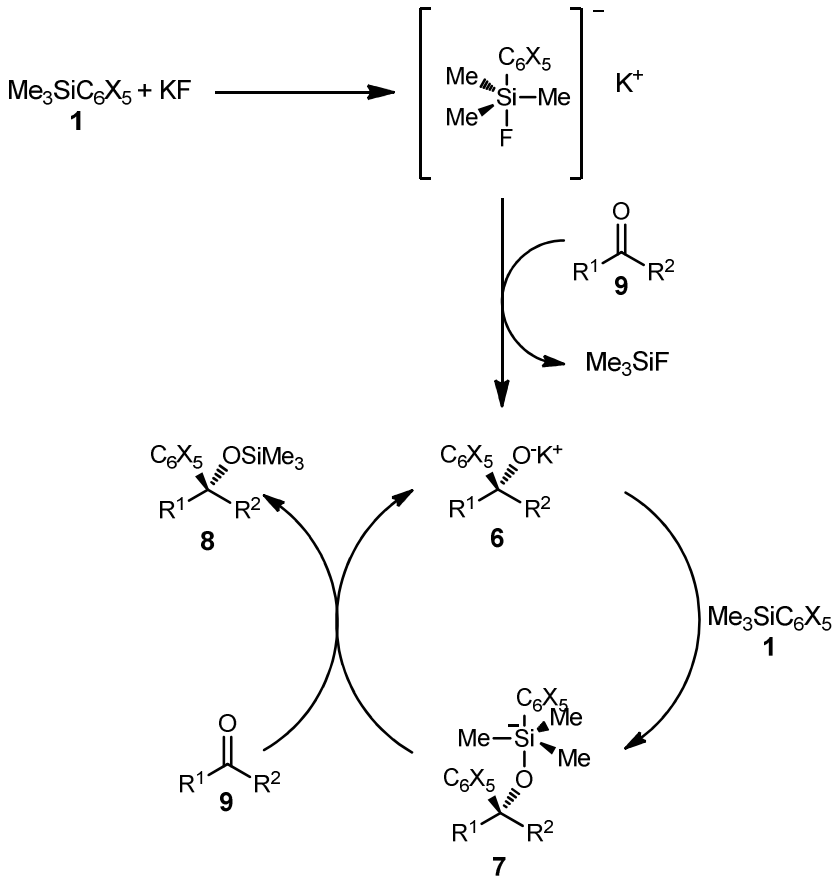
Equation 2.1

In 1972, Ishikawa and Isobe described an improved method for the reaction of polyhalogenophenyltrimethylsilanes with benzaldehyde, employing substoichiometric quantities of potassium fluoride in DMF as an initiator (**Scheme 2.1**).[21] Their reactions went to completion after only a few minutes and although they do not report the reaction of **1** itself in this manner, the yields for the silane reagents that they do report are similar to that obtained by Gilman (43-68%).



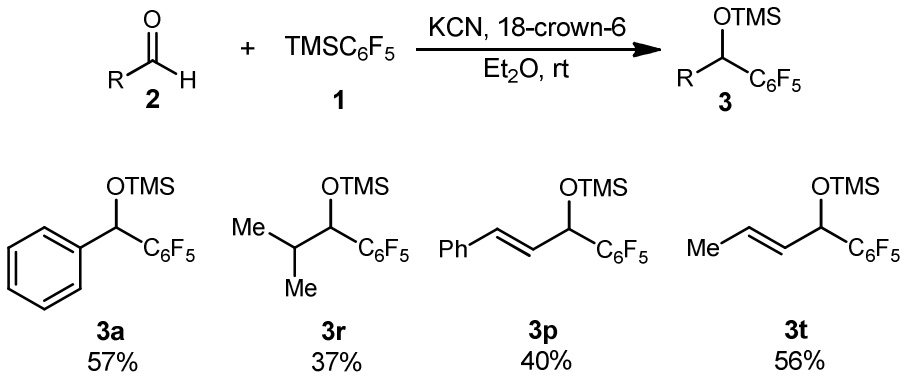
Scheme 2.1

It is highly likely that the mechanism for this process is analogous to that for the reaction of Ruppert's reagent with aldehydes (**Scheme 2.2**). The activation of **1** by the fluoride anion proceeds as has been previously described and the polyhalogenophenyl group is transferred to the electrophilic carbon of the carbonyl group to generate an alkoxide adduct (**6**). The affinity of the silicon atom in **1** for the anionic oxygen of the alkoxide leads to the formation of another pentavalent silicon complex (**7**). The polyhalogenophenyl group is then transferred from this complex to the electrophilic carbon of a carbonyl group, generating another molecule of **6** and the desired product (**8**)**.** The cycle can continue until all of the carbonyl starting material has reacted.



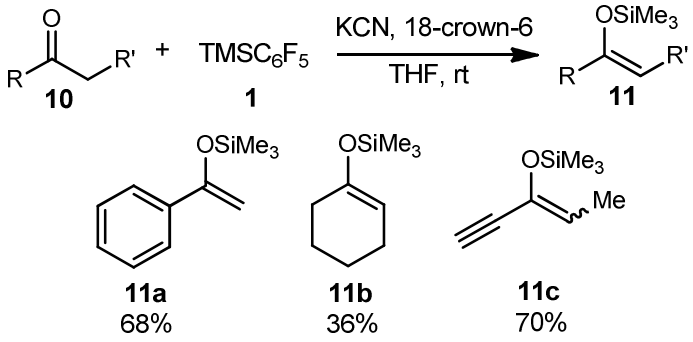
Scheme 2.2

Significantly improved yields (87% for **5a**) were reported by Hiyama and co-workers by changing the activator to tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and the solvent to THF.[22] The use of a potassium cyanide-18-crown-6 complex as the initiator has also been reported.[23] Here, the reaction has been applied to a much wider range of aldehyde substrates, although the yields are fairly poor (**Scheme 2.3**).



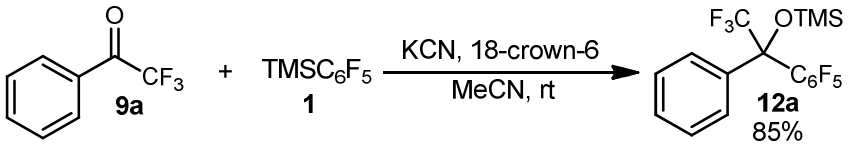
Scheme 2.3

The authors also describe an attempt to extend the scope to include enolisable ketones. However, the products of this reaction are simply the corresponding silyl enol ethers (**Scheme 2.4**).



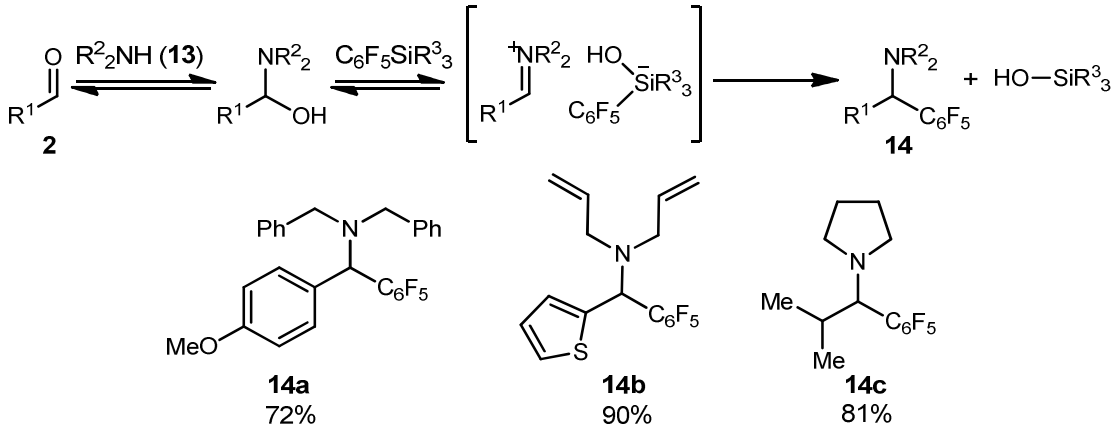
Scheme 2.4

In a later publication,[24] the same authors describe just one non-enolisable ketone substrate for which the pentafluorophenylation reaction using **1** was successful: trifluoroacetophenone (**Equation 2.2**). Other non-enolisable substrates such as octofluoroacetophenone and ^{t}butyl ketone did not undergo any reaction under the same conditions.



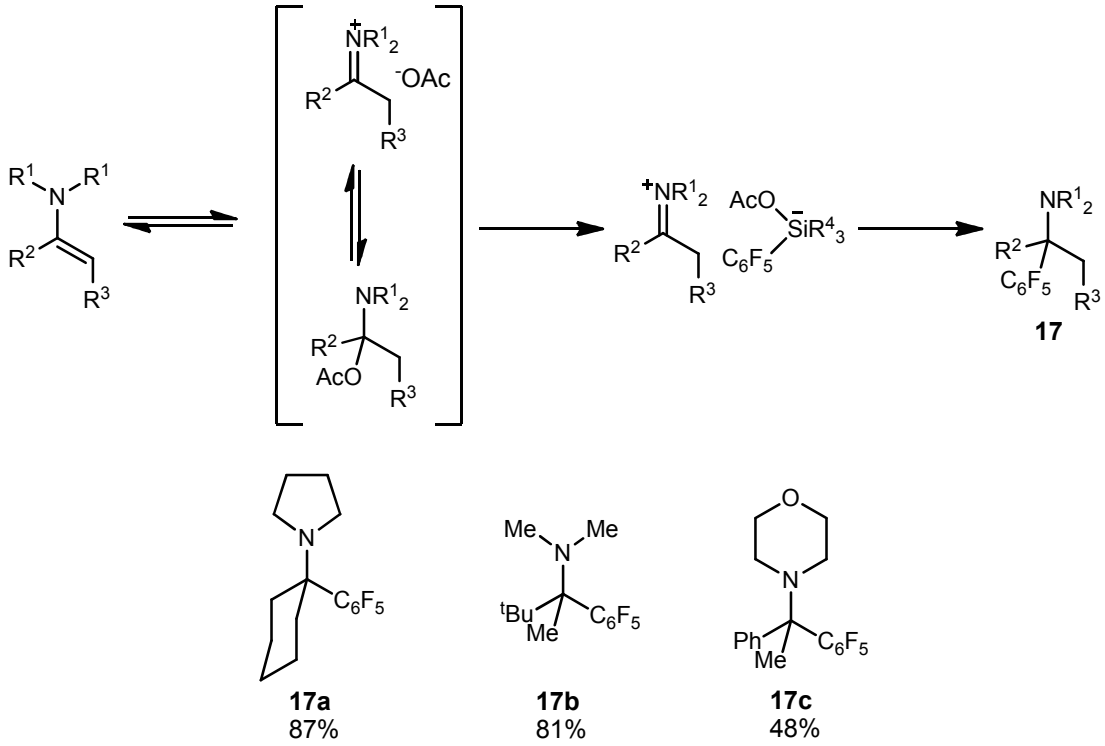
Equation 2.2

Much research has been carried out recently by Dilman's group into reactions of silicon-based pentafluorophenyl reagents with C=N bonds. The products in all of these cases are α-pentafluorophenyl-substituted amines, although the required starting materials vary. Their first report describes the synthesis of pentafluorophenylmethylamines **14** through a silicon Mannich reaction (**Scheme 2.5**).[25] Screening of silicon reagents revealed that **1** is not nucleophilic enough to be used in this reaction and $MeOSi(C_6F_5)_3$ (**15**) was selected instead. The scope of the reaction was explored, changing both the carbonyl and amine component, and revealing ketones to be unreactive in this process.



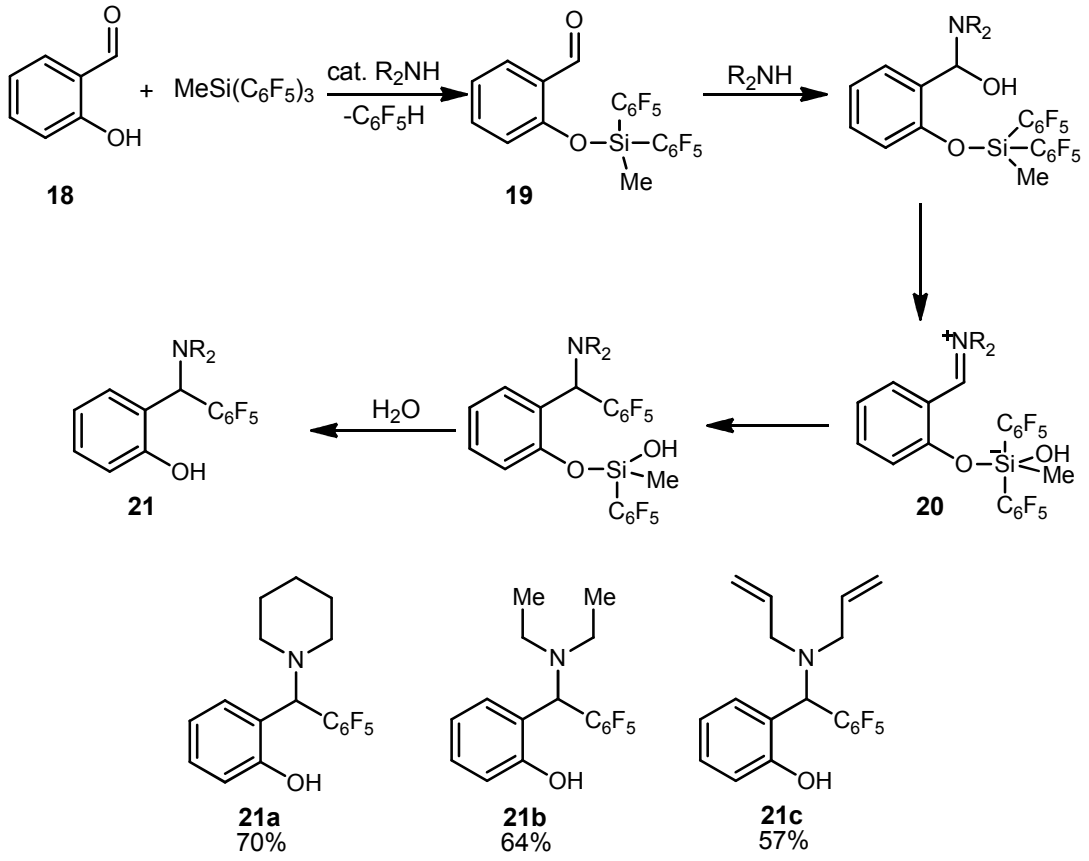
Scheme 2.5

A few months later, the authors published an alternative method, which allows the synthesis of products with quaternary carbon centres (**Scheme 2.6**).[26] This was not possible under the previous conditions, due to the lack of reactivity of ketones. Here, the substrates were preformed enamines, and $MeSi(C_6F_5)_3$ (**16**) was found to be the preferred pentafluorophenylating agent. Acetic acid was employed to generate an iminium acetate from the enamine and the reaction then proceeded as before.



Scheme 2.6

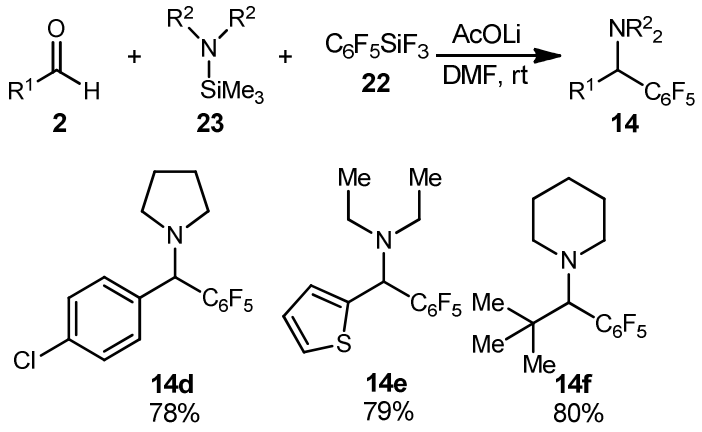
Dilman next reported the use of salicylaldehyde (**18**) in the silicon Mannich reaction (**Scheme 2.7**).[27] The adjacent hydroxyl group allows the reaction to take place under the original conditions but using $MeSi(C_6F_5)_3$ as the pentafluorophenylsilyl derivative. This reagent is preferred to $MeOSi(C_6F_5)_3$ as it is easier to prepare and less sensitive to hydrolysis. The mechanism proposed by the authors is given in **Scheme 2.7**. Reaction of salicylaldehyde with $MeSi(C_6F_5)_3$ generates the silyl ether (**19**), which in turn reacts with the amine to generate a zwitterionic species (**20**). The pentafluorophenyl group is then transferred intramolecularly from silicon to the electrophilic carbon of the iminium cation. After hydrolysis, the desired product (**21**) is obtained.



Scheme 2.7

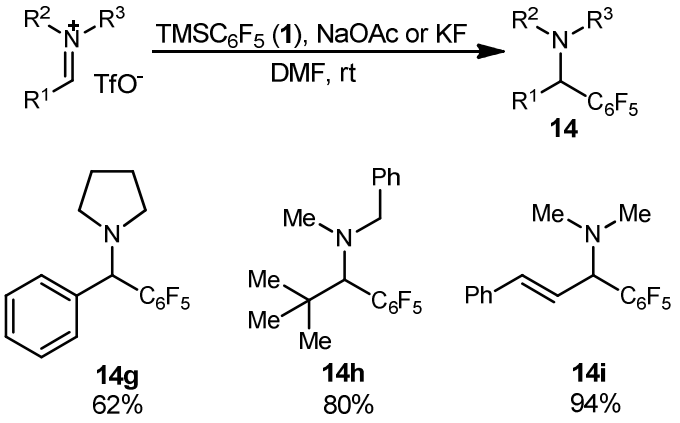
Aldehydes without a neighbouring hydroxyl group were also shown to undergo reaction with TMS-protected amines and a less expensive silicon-based pentafluorophenylating reagent, $C_6F_5SiF_3$ (**22**, **Scheme 2.8**).[28] However, yields did not exceed 27% until a Lewis base, such as lithium acetate, was added into the reaction mixture. The authors attributed this observation to the generation of $F_3SiOSiMe_3$ as a product of the reaction, as it can form an acetal with the

benzaldehyde starting material, thus preventing further reaction. The addition of a Lewis base prevents the formation of this product.



Scheme 2.8

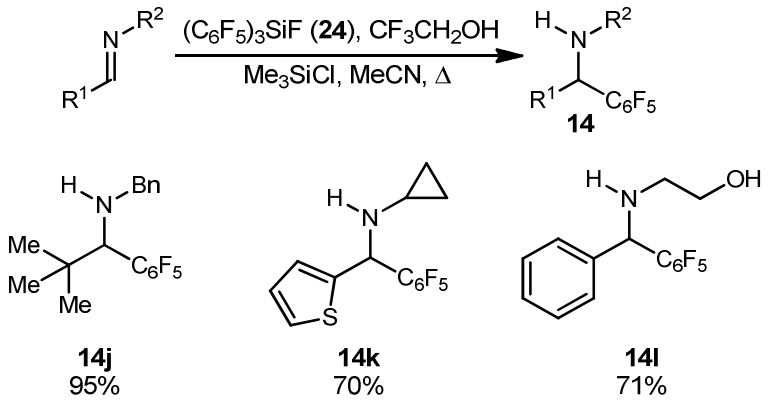
Finally, in 2008, Dilman and co-workers reported the first use of **1** itself in these reactions.[29] This method requires the initial generation of iminium ions either from imines or from the reaction of aldehydes and amines *in situ*, as before. The pentafluorophenylating agent **1** was then added along with a Lewis base, the most effective of which was found to be potassium fluoride or sodium acetate (**Scheme 2.9**). The yields for this process are generally excellent and reaction times never exceeded 2 hours.



Scheme 2.9

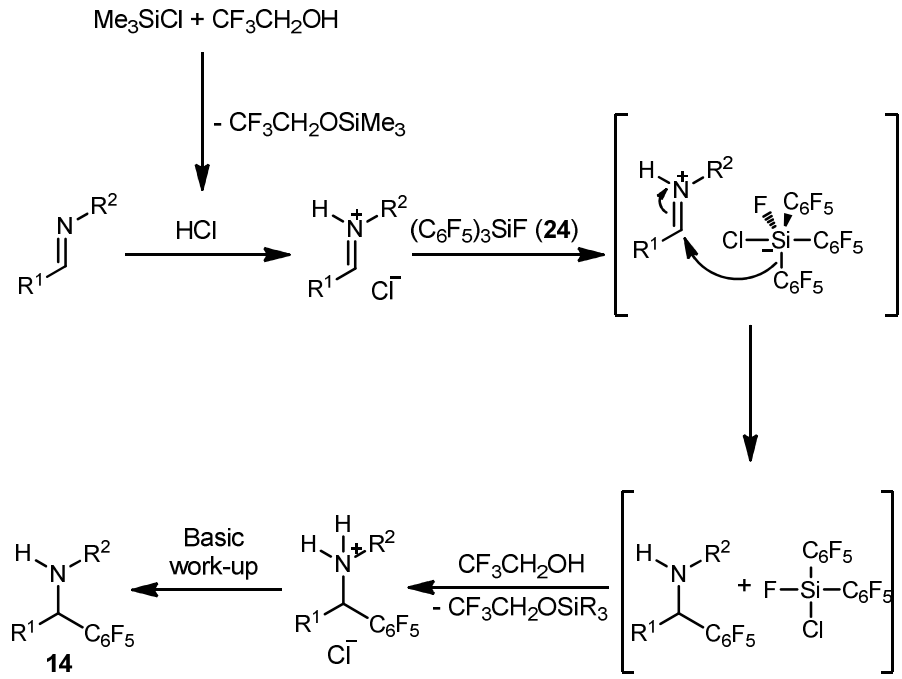
Preformed imines can also be pentafluorophenylated to generate α-pentafluorophenyl-substituted amines (**Scheme 2.10**).[30] Here, fluorotris(pentafluorophenyl)silane (**24**), a silicon-based reagent that is more sensitive towards Lewis-base activation than **1**, was used. With

this reagent, even chloride anions, which are not particularly nucleophilic, could mediate the reaction of **24** with non-activated imines. The optimised conditions for the reported reaction employed 2,2,2-trifluoroethanol, chlorotrimethylsilane and heating under reflux in acetonitrile. A wide range of imine substrates underwent reaction in this manner to provide high yields of the desired product (**14**) in under one hour. Diaryl imines required a higher concentration of chloride ions, supplied by benzyltriethylammonium chloride, for the reaction to complete.



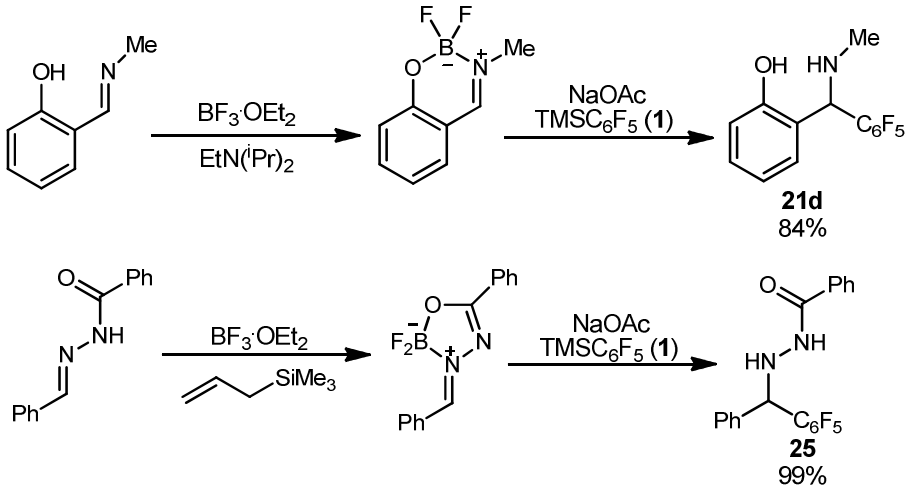
Scheme 2.10

The proposed mechanism for this process is given in **Scheme 2.11**. The reaction of chlorotrimethylsilane with the alcohol generates anhydrous HCl, which subsequently protonates the imine to give an iminium cation. The chloride anion then associates with the silicon atom of **24** generating a pentavalent silicon complex, which transfers a pentafluorophenyl group to the electrophilic carbon of the iminium ion. Two equivalents of acid are required due to the greater basicity of the amine product, relative to the imine.



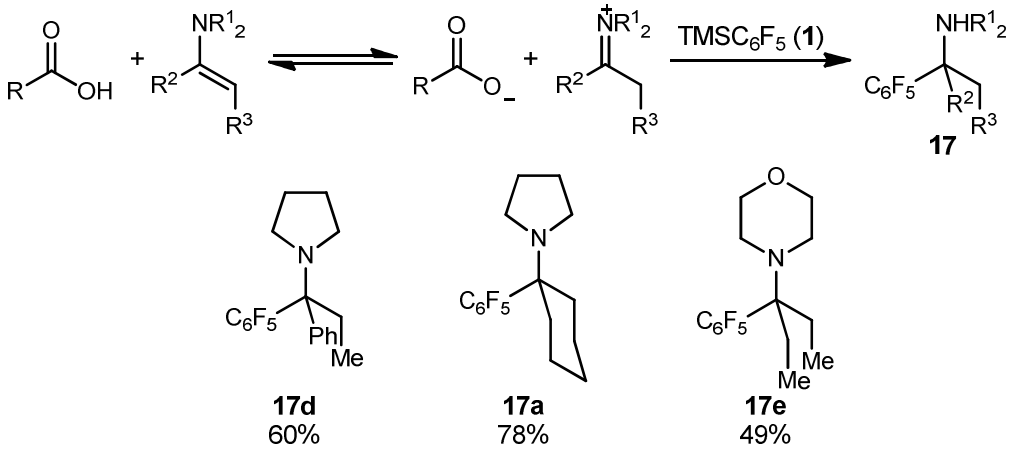
Scheme 2.11

When Dilman and co-workers reported the trifluoromethylations of salicyl aldimines[31] and *N*-benzoylhydrazones[32] using Ruppert's reagent, $TMSCF_3$, the methods were also applied to the introduction of the pentafluorophenyl group (**Scheme 2.12**). Both of these methods employ complexation of a Lewis acid as a means of increasing the electrophilicity of an imine. The authors observe that the problem with this approach is that fluoroalkyl silanes require Lewis basic activation and if a Lewis acid is added to the reaction mixture, this activation will not occur. The solution was found to be intramolecular chelation with an adjacent hydroxyl group. In this manner, the authors achieved the pentafluorophenylation of salicyl aldimines and *N*-benzoylhydrazones in excellent yields using boron trifluoride and sodium acetate as the Lewis acid and Lewis base respectively.



Scheme 2.12

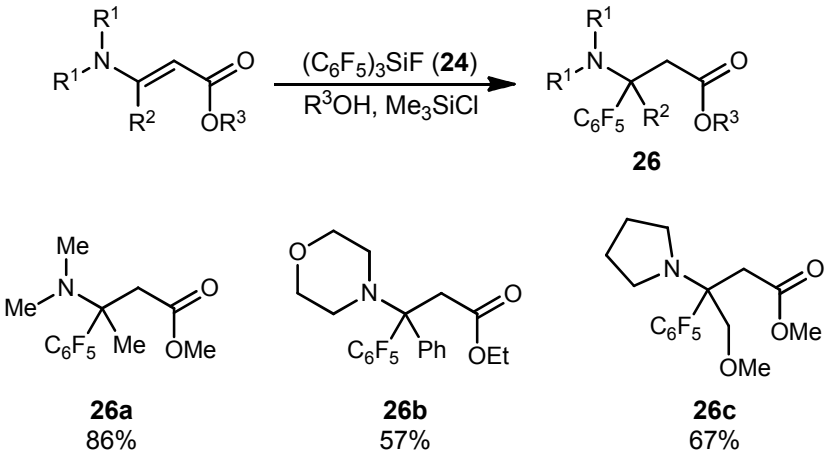
Enamines have also been pentafluorophenylated using the commercially available pentafluorophenylating agent **1**.[33] Again, the method used was developed by Dilman and co-workers for use with Ruppert's reagent and extended to **1** (**Scheme 2.13**). The report describes the synthesis of α-pentafluorophenylated amines using **1** and a carboxylic acid. The first step of this reaction is shown in **Scheme 2.13**. The carboxylic acid can protonate the enamine to generate an iminium cation and a carboxylate anion. The carboxylate anion then acts as the nucleophilic activator for **1** and the mechanism proceeds as it would for any other activator.



Scheme 2.13

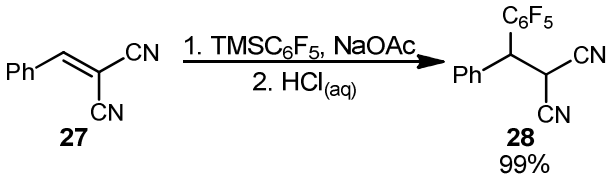
This methodology has been extended further to include the pentafluorophenylation of β-aminoacrylates (**Scheme 2.14**).[34] However, in this case, $(C_6F_5)_3SiF$ was used to transfer the C_6F_5 group and a stronger acid, such as HCl generated *in situ* from an alcohol and

chlorotrimethylsilane, is required. The yields for this process vary greatly depending upon the substituents on the enamine. For example, when R^2 is a phenyl group, yields decrease significantly relative to those obtained when there is a methyl substituent in that position. This is presumably due to increased steric hindrance.



Scheme 2.14

The development of methods for the use of fluoroalkyl silane reagents in conjugate additions has proved to be much more difficult and reports are very limited. However, in 2008 Dilman reported the conjugate pentafluorophenylation of an arylidene malononitrile **27** requiring stoichiometric sodium acetate in DMF (**Equation 2.3**).[35] Whilst this is the only example given in the publication, the yield is excellent at 99%.



Equation 2.3

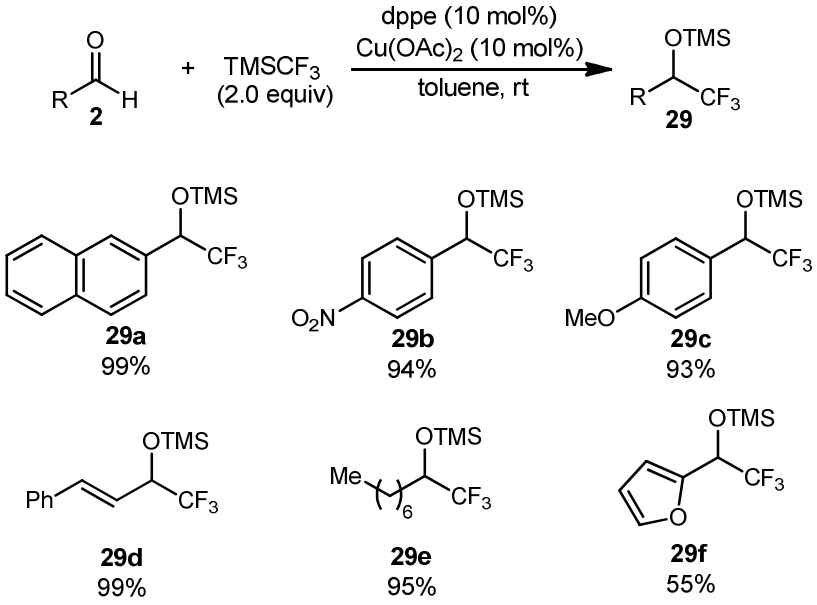
In summary, (pentafluorophenyl)trimethylsilane is a versatile reagent and can be used in the nucleophilic pentafluorophenylation of a range of C=N electrophiles. However, the corresponding reactions of carbonyl compounds are less common. Existing studies of the pentafluorophenylation of aldehydes using **1** contain limited descriptions of substrate scope and there is only one example of the successful reaction of a ketone. A more detailed

evaluation of the scope of the pentafluorophenylation of aldehydes and ketones using **1** under mild conditions and employing relatively non-toxic reagents is therefore warranted.

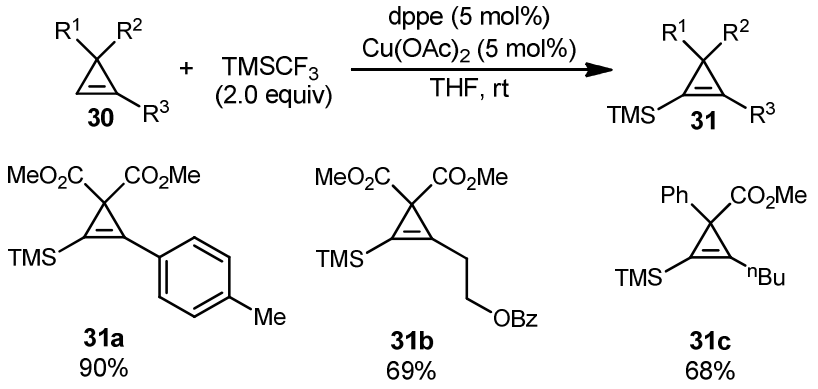
2.2 Results and Discussion

As we have seen, (pentafluorophenyl)trimethylsilane has been employed in the pentafluorophenylation of C=N bonds using a variety of methods, whilst the corresponding reactions with carbonyl compounds are less common. On this basis, we have carried out a more detailed evaluation of the scope of pentafluorophenylation of aldehydes and ketones using **1** under user-friendly conditions.

In considering potential reagents to promote carbonyl pentafluorophenylation using **1**, we were prompted to examine copper-dppe complexes, in view of their successful use in combination with the Ruppert-Prakash reagent for the trifluoromethylation of aldehydes (**Scheme 2.15**)[36] and the direct silylation of bisactivated cyclopropenes conducted within the Lam group (**Scheme 2.16**).[37]

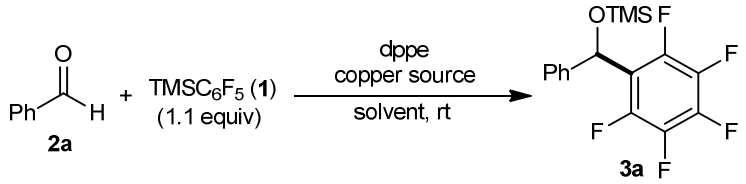


Scheme 2.15



Scheme 2.16

For our initial investigations, benzaldehyde (**2a**) was employed as a test substrate. The results of a brief study of reaction parameters is given in **Table 2.1**.



Entry	Copper Source	Copper Loading (mol%)	Solvent	Conversion (%)	Reaction Time (h)
1	$Cu(OAc)_2$	10	THF	>95	1.5
2	$Cu(acac)_2$	10	THF	90	21
3	$Cu(OAc)_2$	5	THF	80	6
4	$Cu(OAc)_2$	10	toluene	<5	2

Table 2.1

It is interesting to observe that the use of toluene in this reaction gave minimal (<5%) conversions despite its use by Shibata and co-workers[36] in their analogous trifluoromethylation procedure (**Entry 4**). The conditions that were selected as effective for carbonyl pentafluorophenylation as a result of this screening were $Cu(OAc)_2$ (10 mol%), dppe (10 mol%) and $TMSC_6F_5$ (1.1 equiv) in THF at room temperature. After the reaction had stopped progressing, as observed by TLC analysis, a solution of HCl was added to deprotect the TMS ether that is the initial product of pentafluorophenylation.

Table 2.2 presents the results of pentafluorophenylation of a range of unsaturated aldehydes under these conditions.

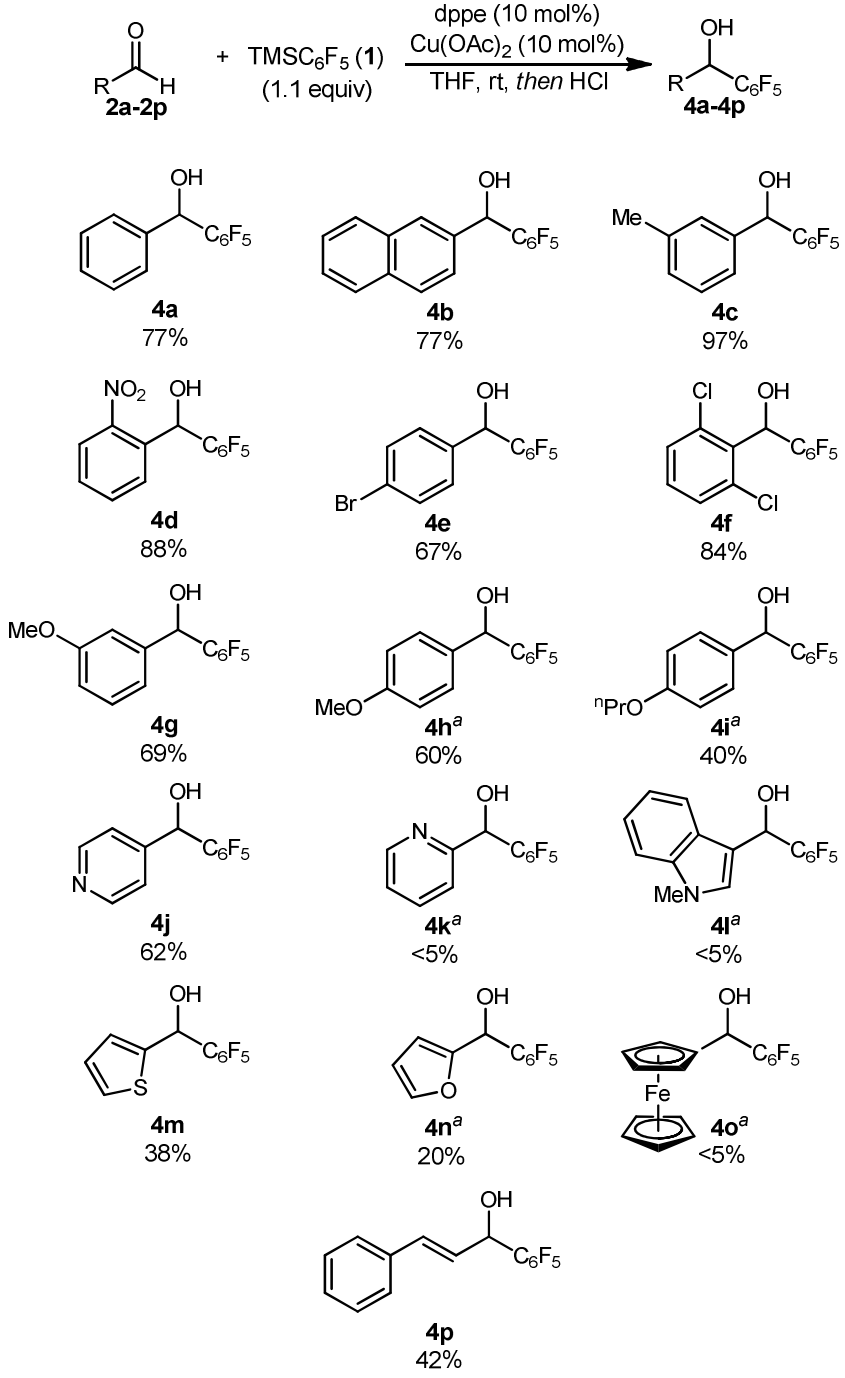


Table 2.2 Yields stated are of isolated product. [a] Conversion as determined by ^{1}H and ^{19}F NMR.

The yields obtained for the reaction of aromatic aldehydes (**2a-i**) were generally good. Substitution at any ring position was well tolerated and substrates containing electron-withdrawing substituents (particularly in *ortho* positions e.g. **2d** and **2f**) were shown to give

increased yields of isolated product (**4d** and **4f**). On the other hand, substrates containing alkoxy substituents on the aromatic rings (**2g-i**) were shown to give lower conversions. Heating reactions that did not complete gave no more desired product and after prolonged periods of heating, degradation of starting materials and products began to be observed. Increasing catalyst loading and increasing the concentration of the reaction mixture also failed to increase the quantity of desired product that formed.

Heteroaromatic aldehydes were more problematic. 2-Furancarboxaldehyde (**2n**) showed only 20% conversion and 1-methylindole-2-carboxaldehyde (**2l**) gave less than 5% of the desired product. Again, increasing the reaction temperature failed to give an improvement in the observed conversion. The reaction of 2-pyridinecarboxaldehyde (**2k**) resulted in a complex mixture of products with no starting material remaining after only 5 minutes of reaction. No desired product was isolated from the crude reaction mixture. However, 4-pyridinecarboxaldehyde (**2j**) did provide the desired product **4j** in 62% yield, while 2-thiophenecarboxaldehyde (**2m**) gave **4m** in 38% yield.

Trans-cinnamaldehyde was used as an example of an α,β-unsaturated aldehyde substrate. Conversions were found to be poor for this substrate as well, giving a 42% yield. As in previous examples, heating failed to give an improvement, but did lead to the appearance of side-products, which were not identified. No formation of the conjugate addition product was observed.

Aliphatic aldehydes were found to be very reactive under the optimised conditions and complete consumption of starting material was generally observed after a reaction time of only fifteen minutes. However, these reactions also provided a number of unidentified side products resulting in greatly decreased isolated yields (34% for **4q**). Decreasing the reaction temperature to −78 °C offered some improvement in minimising side-product formation, but isolated yields of the products **4q**-**4s** (**Table 2.3**) remain modest due to varying levels of decomposition. Slow addition of the (pentafluorophenyl)trimethylsilane reagent or of the aldehyde offered no further increase in yields.

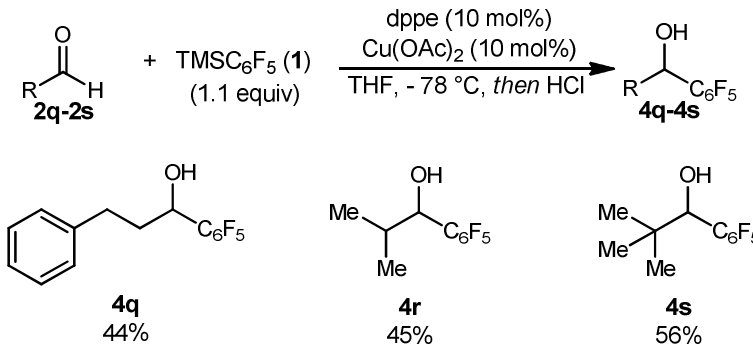
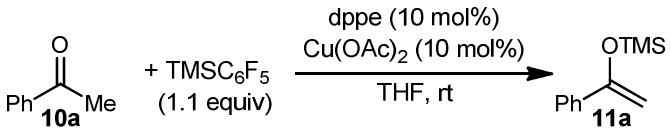


Table 2.3 Yields given are of isolated product.

Extension of this protocol to more challenging ketone substrates was then explored. With enolisable ketones, such as acetophenone, only conversion into the corresponding trimethylsilyl enol ether was obtained, which is consistent with previous reports (**Equation 2.4**).[23]



Equation 2.4

With benzophenone, a non-enolisable substrate, no reaction was obtained. However, more electrophilic ketones such as ethyl pyruvate and 4-nitrobenzophenone did lead to the desired products **12b** and **12c**, respectively, though in modest yields (**Table 2.4**).

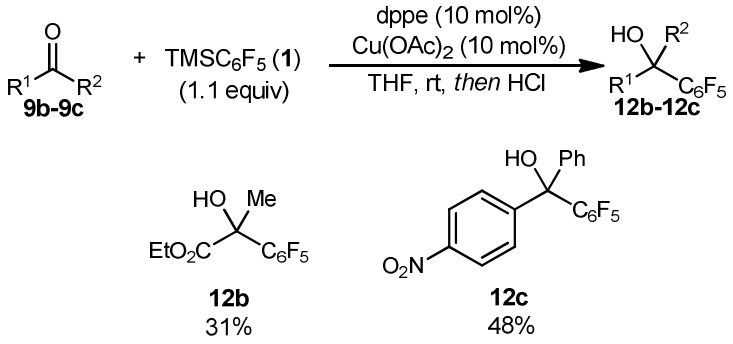
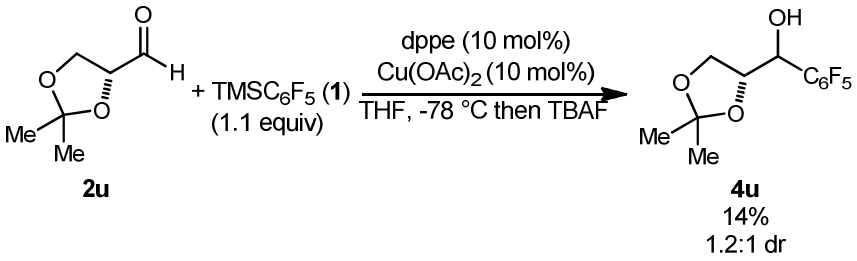


Table 2.4 Yields given are of isolated product.

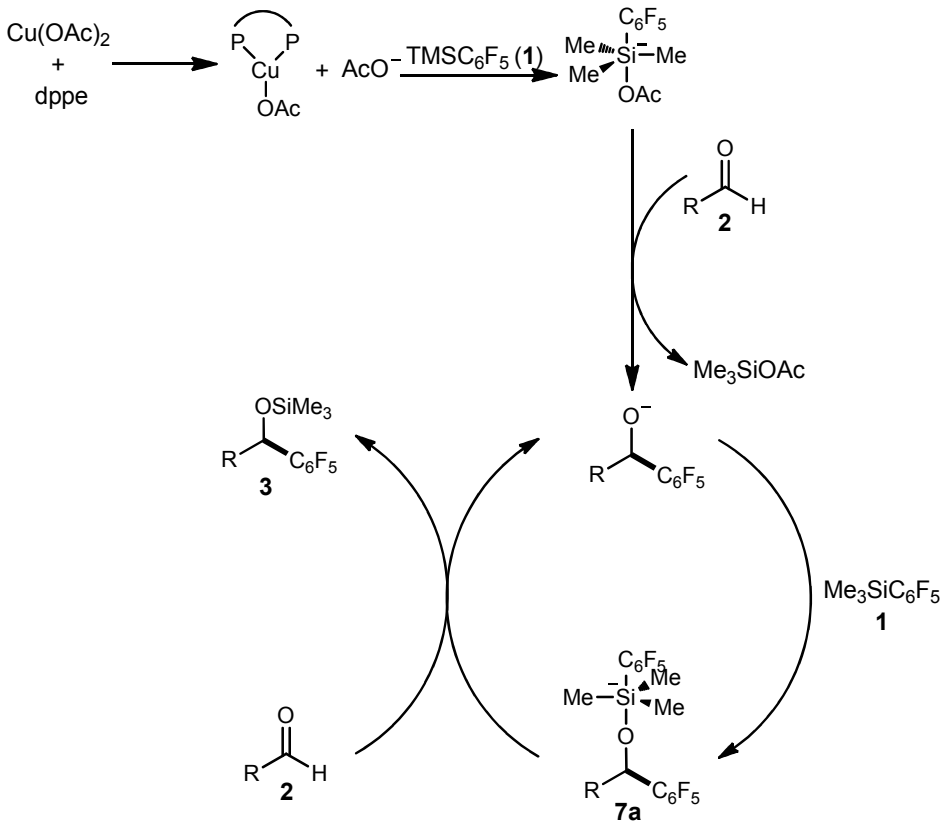
Other conditions were also attempted for the pentafluorophenylation of ketones, including the use of such Lewis acids as $Ti(OiPr)_4$, and MgF_2, as well as tetrabutylammonium triphenyldifluorosilicate (TBAT). Various solvents and temperatures were tried with activators in both catalytic and stoichiometric quantities. No significant amount of pentafluorophenylation of acetophenone was observed under any of the conditions tried.

The reaction of an enantiomerically pure aldehyde was investigated to ascertain whether any diastereoselectivity was observed under the optimised conditions. Unfortunately, as for all aliphatic aldehydes, a large amount of degradation products were obtained along with only a 14% yield of isolated product even when the reaction was conducted at -78 °C. The diastereomers were obtained in a 1.2:1 ratio.



Equation 2.5

The exact role of $Cu(OAc)_2$ and dppe in promoting carbonyl pentafluorophenylation is not clearly understood at this stage. However, our current hypothesis is that the $Cu(OAc)_2$-dppe complex merely serves to initiate an autocatalytic process in direct analogy to mechanisms proposed for carbonyl trifluoromethylation using the Ruppert-Prakash reagent ($TMSCF_3$). This is illustrated in **Scheme 2.17**.



Scheme 2.17

As it is not believed that the copper is involved in the reaction mechanism beyond the release of an acetate anion, developing a set of conditions for the enantioselective reaction using copper-bisphosphine catalysis was unlikely to be as simple as employing a chiral bisphosphine ligand. However, a brief screen of chiral non-racemic bisphosphine ligands (including Josiphos, BINAP and Chiraphos) was conducted under the optimised conditions in order to determine if any enantioselectivity was observed. For none of the ligands employed was any enantiomeric excess obtained, although the amount of conversion to product did differ from one ligand to another. This result agrees with a report by Shibata[38] on his group's attempts to carry out an asymmetric trifluoromethylation reaction using Ruppert's reagent and copper-bisphosphine catalysis.

2.3 Conclusions

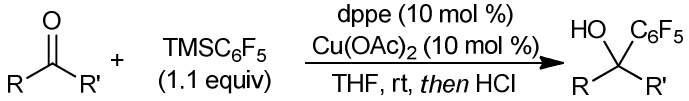
In summary, we have developed a set of mild conditions for the pentafluorophenylation of carbonyl compounds using copper-bisphosphine initiation of (pentafluorophenyl)trimethylsilane. The conditions work well for aromatic aldehydes and give modest product yields for the reaction of aliphatic aldehydes and particularly electrophilic ketones.[39] Attempts to carry out the reaction asymmetrically through the use of chiral bisphosphine ligands failed to give any enantioselectivity.

2.4 Experimental

General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. THF and toluene were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontoursolventsystems.com. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate solution. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[40] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a Nujol mull. ^{1}H NMR spectra were recorded on a Bruker DMX500 (500 MHz) spectrometer or a Bruker DPX360 (360 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm; CD_3OD at 4.84 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm; CD_3OD at 49.05 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. ^{19}F NMR spectra were recorded on a Bruker ARX250 (235 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield of $CFCl_3$, using fluorobenzene as internal standard (C_6H_5F at –113.2 ppm). High-resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea.

General Procedure A for Pentafluorophenylation of Aldehydes and Ketones



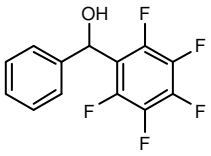
A solution of $Cu(OAc)_2$ (18.2 mg, 0.10 mmol) and dppe (39.8 mg, 0.10 mmol) in THF (3 mL) was stirred at room temperature for 30 min. The appropriate aldehyde or ketone (1.00 mmol) was then added, followed by $TMSC_6F_5$ (210 μL, 1.10 mmol) over 0.5 min and the reaction was stirred at room temperature until complete consumption of the carbonyl compound as observed by TLC analysis, or until no further reaction progress could be seen. (In the case of aliphatic aldehydes, the mixture was cooled to −78 °C before the addition of $TMSC_6F_5$ and the reaction was thereafter maintained at −78 °C.) The reaction was quenched with 1 mL HCl solution (~ 1M in $MeOH/H_2O$, made up by diluting 8.2 mL of 37% HCl up to 100 mL with MeOH) and the mixture was stirred at room temperature for 1 h. The mixture was filtered through a short plug of SiO_2 using EtOAc (*ca*. 50 mL) as eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired alcohol.

General Procedure B for Pentafluorophenylations of Aldehydes and Ketones

The procedure was identical to General Procedure A, except that the appropriate aldehyde or ketone were stirred together with the solution of $Cu(OAc)_2$ and dppe for 30 min prior to the addition of $TMSC_6F_5$.

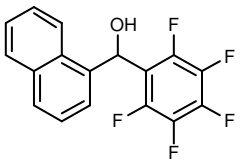
General Procedure C for Pentafluorophenylations of Aldehydes and Ketones

This procedure was identical to procedure A except that the workup was altered as follows: When the reaction had stopped progressing as observed by TLC analysis, 1 mL of HCl (~ 1M in $MeOH/H_2O$, made up by diluting 8.2 mL of 37% HCl up to 100 mL with MeOH) was added and the mixture was stirred for 1 h. The solvent was removed *in vacuo* and the resulting mixture was partitioned between saturated aqueous $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired alcohol.



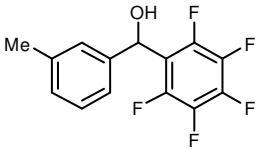
(Pentafluorophenyl)phenylmethanol (4a)[22]

The title compound was prepared according to General Procedure A from benzaldehyde (102 μL, 1.00 mmol) for a reaction time of 2 h and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil, which solidified to a white solid upon standing (210 mg, 77%). R_f = 0.32 (10% EtOAc/hexane); m.p. 38-41 °C (lit[22] m.p. 49 °C); IR (Nujol) 3252 (OH), 1654, 1522, 1504, 1456, 1302, 1120, 994, 945, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.32 (5H, m, Ar**H**), 6.22 (1H, s, C**H**OH), 3.32 (1H, br, O**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.6 (2 x C, dm, *J* = 241.9 Hz), 140.7 (C, dm, *J* = 241.0 Hz), 140.4 (C), 137.6 (2 x C, dm, *J* = 253.2 Hz), 128.7 (2 x CH), 128.2 (CH), 125.3 (2 x CH), 116.8 (C, t, *J* = 17.0 Hz), 67.4 (CH); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.1 (2F, dd, *J* = 21.7, 7.6 Hz, Ar**F**), –154.6 (1F, t, *J* = 21.2 Hz, Ar**F**), –161.5 (2F, ddd, *J* = 21.7, 21.2, 7.6 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{13}H_7F_5O$ [M^+]: 274.0412, found: 274.0413.



Naphthalen-1-ylpentafluorophenylmethanol (4b)

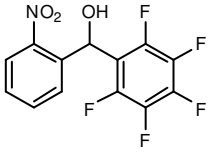
The title compound was prepared according to General Procedure A from 1-naphthaldehyde (136 μL, 1.00 mmol) for a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give white crystals (250 mg, 77%). R_f = 0.23 (10% EtOAc/hexane); m.p. 104-107 °C; IR (Nujol) 3321 (OH), 1651, 1522, 1500, 1119, 1082, 992, 940, 798, 776 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.07 (1H, dd, *J* = 8.3, 1.8 Hz, Ar**H**), 7.91 (1H, dd, *J* = 7.6, 1.8 Hz, Ar**H**) 7.87 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.63 (1H, d, *J* = 7.2 Hz, Ar**H**), 7.60-7.46 (3H, m, Ar**H**), 6.89 (1H, s, C**H**OH), 2.87 (1H, br, O**H**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 144.9 (2 x C, dm, *J* = 249.4 Hz), 140.8 (C, dm, *J* = 254.8 Hz), 137.6 (2 x C, dm, *J* = 253.5 Hz), 134.8 (C), 133.7 (C), 130.2 (C), 129.3 (CH), 128.9 (CH), 126.7 (CH), 125.9 (CH), 125.0 (CH), 123.8 (CH), 122.5 (CH), 115.9 (C, t, *J* = 14.4 Hz), 65.0 (CH); ^{19}F NMR (235 MHz, $CDCl_3$) δ –142.1 (2F, dd, *J* = 21.4, 7.2 Hz, Ar**F**), –154.3 (1F, t, *J* = 21.2 Hz, Ar**F**), –161.4 (2F, ddd, *J* = 21.4, 21.2, 7.2 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{17}H_9F_5O$ [M^+]: 324.0568, found: 324.0570.



Pentafluorophenyl-*m*-tolylmethanol (4c)

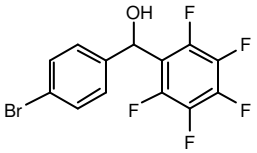
The title compound was prepared according to General Procedure A from *m*-tolualdehyde (118 μL, 1.00 mmol) for a reaction time of 3 h and purified by column chromatography (10% EtOAc/hexane) to give white crystals (280 mg, 97%). R_f = 0.26 (10% EtOAc/hexane); m.p. 62-65 °C; IR (Nujol) 3289 (OH), 1654,

1608, 1522, 1502, 1301, 1118, 1045, 992, 955 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.27 (1H, dd, *J* = 7.6, 7.6 Hz, Ar**H**), 7.20 (1H, s, Ar**H**), 7.19 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.14 (1H, d, *J* = 7.6 Hz, Ar**H**) 6.19 (1H, s, C**H**OH), 2.85 (1H, br, O**H**), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 144.6 (2 x C, dm, *J* = 249.2 Hz), 140.7 (C, dm, *J* = 254.6 Hz), 140.5 (C), 138.6 (C), 137.6 (2 x C, dm, *J* = 253.3 Hz), 129.0 (CH), 128.6 (CH), 126.0 (CH), 122.3 (CH), 117.0 (C, t, *J* = 15.2 Hz), 67.6 (CH), 21.4 (CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.1 (2F, dd, *J* = 21.8, 7.6 Hz, Ar**F**), –154.9 (1F, t, *J* = 21.3 Hz, Ar**F**), –161.6 (2F, ddd, *J* = 21.8, 21.3, 7.6 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{14}H_9F_5O$ [M^+]: 288.0568, found: 288.0566.



(2-Nitrophenyl)pentafluorophenylmethanol (4d)[41]

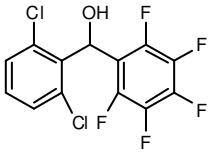
The title compound was prepared according to General Procedure B from 2-nitrobenzaldehyde (151 mg, 1.00 mmol) for a reaction time of 3 h and purified by column chromatography (10% EtOAc/hexane) to give a yellow oil (281 mg, 88%). R_f = 0.17 (10% EtOAc/hexane); IR (film) 3438 (OH), 1654, 1611, 1578, 1503 (NO_2), 1347 (NO_2), 1304, 1119, 996, 951 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.09 (1H, d, *J* = 8.3 Hz, Ar**H**), 8.06 (1H, d, *J* = 8.3 Hz, Ar**H**) 7.75 (1H, t, *J* = 7.7 Hz, Ar**H**), 7.54 (1H, t, *J* = 7.7 Hz, Ar**H**), 6.81 (1H, s, C**H**OH), 3.35 (1H, br, O**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 146.6 (C), 145.1 (2 x C, dm, *J* = 255.2 Hz), 140.7 (C, dm, *J* = 249.7 Hz), 135.8 (C), 134.9 (2 x C, dm, *J* = 248.0 Hz), 133.8 (CH), 129.1 (CH), 128.7 (CH), 125.1 (CH), 115.6 (C, t, *J* = 14.8 Hz), 63.9 (CH); ^{19}F NMR (235 MHz, $CDCl_3$) δ –141.5 (2F, dd, *J* = 21.0, 6.8 Hz, Ar**F**), –153.6 (1F, t, *J* = 20.7 Hz, Ar**F**), –161.5 (2F, ddd, *J* = 21.0, 20.7, 6.8 Hz, Ar**F**); *m/z*: No mass ion peaks observed under a range of mass spectroscopic techniques.



(4-Bromophenyl)pentafluorophenylmethanol (4e)

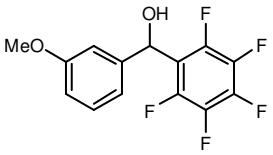
The title compound was prepared according to General Procedure B from 4-bromobenzaldehyde (185 mg, 1.00 mmol) for a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give yellow crystals (236 mg, 67%). R_f = 0.26 (10% EtOAc/hexane); m.p. 60-63 °C; IR (Nujol) 3318 (OH), 1653, 1525, 1501, 1403, 1123, 1075, 1012, 993, 946 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.4, Ar**H**), 7.13 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.04 (1H, d, *J* = 5.4 Hz, C**H**OH), 3.04 (1H, d, *J* = 5.4 Hz, O**H**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 144.6 (2 x C, dm, *J* = 249.4 Hz), 141.0 (C, dm, *J* = 242.1 Hz), 137.6 (2 x C, dm, *J* = 254.2 Hz), 139.4 (C), 131.8 (2 x CH), 127.0 (2 x

CH), 122.2 (C), 116.3 (C, t, *J* = 14.3 Hz), 66.8 (CH); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.0 (2F, dd, *J* = 21.4, 7.4 Hz, Ar**F**), –153.9 (1F, t, *J* = 21.1 Hz, Ar**F**), –161.1 (2F, ddd, *J* = 21.4, 21.1, 7.4 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{13}H_6BrF_5O$ [M^+]: 351.9517, found: 351.9516.



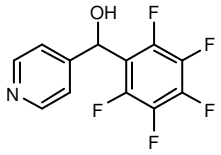
(2,6-Dichlorophenyl)pentafluorophenylmethanol (4f)

The title compound was prepared according to General Procedure B from 2,6-dichlorobenzaldehyde (175 mg, 1.00 mmol) for a reaction time of 5.5 h and purified by column chromatography (8% EtOAc/hexane) to give pale yellow crystals (288 mg, 84%). R_f = 0.27 (10% EtOAc/hexane); m.p. 74-77 °C; IR (Nujol) 3298 (OH), 1651, 1582, 1565, 1523, 1495, 1439, 1120, 999, 939 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.83 (1H, d, *J* = 9.1 Hz, C**H**OH), 3.91 (1H, d, *J* = 9.1 Hz, O**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.8 (2 x C, dm, *J* = 253.3 Hz), 140.6 (C, dm, *J* = 254.4 Hz), 137.5 (2 x C, dm, *J* = 252.9 Hz), 134.8 (C), 134.7 (2 x C), 130.1 (CH), 129.4 (2 x CH), 114.7 (C, t, *J* = 11.9 Hz), 67.7 (CH) ; ^{19}F NMR (235 MHz, $CDCl_3$) δ –141.7 (2F, dd, *J* = 22.2, 7.1 Hz, Ar**F**), –155.0 (1F, t, *J* = 21.5 Hz, Ar**F**), –162.3 (2F, ddd, *J* = 22.2, 21.5, 7.1 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{13}H_5Cl_2F_5O$ [M^+]: 341.9632, found: 341.9631.



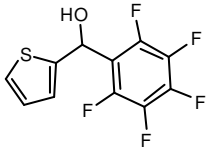
(3-Methoxyphenyl)pentafluorophenylmethanol (4g)

The title compound was prepared according to General Procedure C from *m*-anisaldehyde (122 µL, 1.00 mmol) for a reaction time of 17 h and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil (210 mg, 69%). R_f = 0.18 (10% EtOAc/hexane); IR (film) 3486 (OH), 2360, 1652, 1606, 1588, 1503, 1274, 1228, 1038, 988 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.27 (1H, dd, *J* = 8.1, 7.9 Hz, Ar**H**), 6.98 (1H, br, Ar**H**), 6.92 (1H, d, *J* = 7.9 Hz, Ar**H**), 6.84 (1H, dd, *J* = 8.1, 2.5 Hz, Ar**H**), 6.18 (1H, s, C**H**OH), 3.81 (3H, s, OC**H**$_3$), 3.40 (1H, br, O**H**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 159.8 (C), 142.2 (C), 144.6 (2 x C, dm, *J* = 252.4 Hz), 140.8 (C, dm, *J* = 257.3 Hz), 137.6 (2 x C, dm, *J* = 253.4 Hz), 129.7 (CH), 117.5 (CH), 113.2 (CH), 111.2 (CH), 116.8 (C, t, *J* = 14.8 Hz), 67.2 (CH), 55.1 (CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.0 (2F, dd, *J* = 21.9 Hz, 7.7 Hz, Ar**F**), –154.7 (1F, t, *J* = 21.3 Hz, Ar**F**), –161.5 (2F, ddd, *J* = 21.9 Hz, 21.3 Hz, 7.7 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{14}H_9F_5O_2$ [M^+]: 304.0517, found: 304.0516.



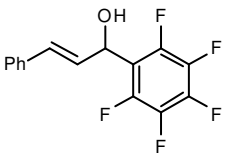
Pentafluorophenylpyridin-4-ylmethanol (4j)

The title compound was prepared according to General Procedure C from 4-pyridinecarboxaldehyde (95 μL, 1.00 mmol) for a reaction time of 17 h and purified by column chromatography (60% EtOAc/hexane) to give yellow crystals (170 mg, 62%). R_f = 0.23 (10% EtOAc/hexane); m.p. 140°C (decomp); IR (Nujol) 3063 (OH), 1651, 1606, 1504, 1414, 1377, 1346, 1222, 1121, 996 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.74 (2H, br, Ar**H**), 7.61 (2H, br, Ar**H**), 6.25 (1H, s, C**H**OH); ^{13}C NMR (90.6 MHz, CD_3OD) δ 153.2 (2 x CH), 149.9 (2 x CH), 146.4 (2 x C, dm, *J* = 249.3 Hz), 142.5 (C, dm, *J* = 252.8 Hz), 139.1 (2 x C, dm, *J* = 251.6 Hz), 118.3 (C, t, *J* = 14.9 Hz), 65.7 (CH), one quaternary peak not detected; ^{19}F NMR (235 MHz, CD_3OD) δ –142.3 (2F, dd, *J* = 19.8, 6.8 Hz, Ar**F**), –155.3 (1F, t, *J* = 19.6 Hz, Ar**F**), –162.6 (2F, ddd, *J* = 19.8, 19.6, 6.8 Hz, Ar**F**); HRMS (ESI) Exact mass calcd for $C_{12}H_7NOF_5$ $[M+H]^+$: 276.0442, found: 276.0444.



(Pentafluorophenyl)thiophen-2-ylmethanol (4m)

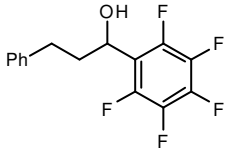
The title compound was prepared according to General Procedure C from 2-thiophenecarboxaldehyde (92 μL, 1.00 mmol) for a reaction time of 4 h and purified by column chromatography (5% EtOAc/hexane) to give yellow crystals (107 mg, 38%). R_f = 0.37 (10% EtOAc/hexanes); m.p. 54-56 °C; IR (Nujol) 3247 (OH), 1654, 1522, 1501, 1302, 1234, 1169, 1117, 992, 939 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18 (1H, dd, *J* = 5.0, 1.0 Hz, Ar**H**), 6.83 (1H, dd, *J* = 5.0, 3.5 Hz, Ar**H**), 6.78 (1H, d, *J* = 3.5 Hz, Ar**H**), 6.24 (1H, d, *J* = 7.8 Hz, C**H**OH), 3.10 (1H, d, *J* = 7.8 Hz, O**H**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 144.6 (2 x C, dm, *J* = 249.8 Hz), 144.1 (C), 140.0 (C, dm, *J* = 255.1 Hz), 137.6 (2 x C, dm, *J* = 253.9 Hz) 127.0 (CH), 126.0 (CH), 124.9 (CH), 116.3 (C, t, *J* = 14.8 Hz), 64.3 (CH); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.0 (2F, dd, *J* = 21.6, 7.6 Hz, Ar**F**), –154.0 (1F, t, *J* = 21.1 Hz, Ar**F**), –161.2 (2F, ddd, *J* = 21.6, 21.1, 7.6 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{11}H_5F_5OS$ $[M^+]$: 279.9976, found: 279.9976.



***(E)*-1-Pentafluorophenyl-3-phenylprop-2-en-1-ol (4p)**[23]

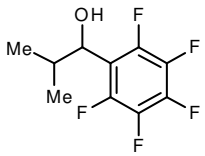
The title compound was prepared according to General Procedure A from trans-cinnamaldehyde (126 μL, 1.00 mmol) for a reaction time of 5 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (127 mg, 42%). R_f = 0.19 (10% EtOAc/hexane); m.p. 116-118 °C; IR (Nujol) 3166 (OH), 1652, 1520,

1498, 1124, 1095, 991, 966, 944, 695 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.26 (5H, m, Ar**H**), 6.69 (1H, d, *J* = 15.8 Hz, PhC**H**=C), 6.52 (1H, ddt, *J* = 15.8, 6.8, 1.5 Hz, PhCH=C**H**), 5.75 (1H, d, *J* = 6.8 Hz, C**H**OH), 2.48 (1H, br, O**H**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 144.7 (2 x C, dm, *J* = 249.3 Hz), 141.2 (C, dm, *J* = 248.3 Hz), 137.6 (2 x C, dm, *J* = 253.3 Hz), 135.6 (C), 132.9 (CH), 128.7 (2 x CH), 128.5 (CH), 127.3 (CH), 126.7 (2 x CH), 116.0 (C, m), 66.9 (CH); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.4 (2F, dd, *J* = 21.8, 7.8 Hz, Ar**F**), –154.8 (1F, t, *J* = 21.2 Hz, Ar**F**), –161.6 (2F, ddd, *J* = 21.8, 21.2, 7.8 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{15}H_9F_5O$ [M^+]: 300.0568, found: 300.0565.



1-Pentafluorophenyl-3-phenyl-propan-1-ol (4q)

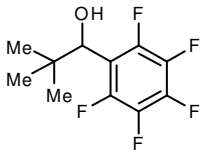
The title compound was prepared according to General Procedure C from hydrocinnamaldehyde (132 μL, 1.00 mmol) for a reaction time of 2.5 h at –78 °C and purified by column chromatography (10% EtOAc/hexane) to give a white solid (132 mg, 44%). R_f = 0.22 (10% EtOAc/hexane); m.p. 70-72 °C; IR (Nujol) 3195 (OH), 2359, 1651, 1521, 1497, 1455, 1304, 1124, 1020, 968 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.32-7.26 (2H, m, Ar**H**), 7.23-7.17 (3H, m, Ar**H**), 5.07 (1H, t, *J* = 7.9 Hz, CHO**H**), 2.88-2.80 (1H, m, C**H**$_2$CH$_2$), 2.66 (1H, ddd, *J* = 14, 9.2, 6.9 Hz, C**H**$_2$CH$_2$), 2.37 (1H, dddd, 14, 9.2, 7.9, 5.6 Hz, CH$_2$C**H**$_2$), 2.21 (1H, br, O**H**), 2.21-2.11 (1H, m, CH$_2$C**H**$_2$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 144.7 (2 x C, dm, *J* = 247.8 Hz), 140.5 (C, dm, *J* = 254.4 Hz), 140.4 (C), 137.5 (2 x C, dm, *J* = 253.0 Hz), 128.5 (2 x CH), 128.3 (2 x CH), 126.2 (CH), 116.9 (C, t, *J* = 15.4 Hz), 65.8 (CH), 38.2 (CH$_2$), 32.1 (CH$_2$); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.8 (2F, dd, *J* = 22.0, 8.0 Hz, Ar**F**), –155.1 (1F, t, *J* = 21.4 Hz, Ar**F**), –161.8 (2F, ddd, *J* = 22.0, 21.4, 8.0 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{15}H_{11}F_5O$ [M^+]: 302.0725, found: 302.0726.



2-Methyl-1-pentafluorophenylpropan-1-ol (4r)

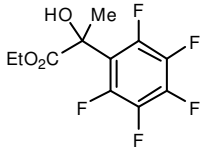
The title compound was prepared according to General Procedure C from isobutyraldehyde (91 μL, 1.00 mmol) for a reaction time of 3 h at –78 °C and purified by column chromatography (8% EtOAc/hexane) to give white crystals (107 mg, 45%). R_f = 0.26 (10% EtOAc/hexanes); m.p. 39-41 °C; IR (Nujol) 3243 (OH), 1652, 1522, 1502, 1302, 1145, 1112, 1043, 995, 967 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.62 (1H, d, *J* = 9.2 Hz, C**H**OH), 2.37 (1H, br, O**H**), 2.16 (1H, m, (CH$_3$)$_2$C**H**), 1.14 (3H, d, *J* = 6.6 Hz, C**H**$_3$), 0.79 (3H, d, *J* = 6.8 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.6 (2 x C, dm, *J* = 245.1 Hz), 140.4 (C, dm, *J* = 253.9 Hz), 137.5 (2 x C, dm, *J* = 252.8 Hz), 116.6 (C, t, *J* = 16.0 Hz),

72.4 (CH), 34.2 (CH), 19.2 (CH_3), 18.7 (CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.0 (2F, dd, *J* = 22.1, 7.9 Hz, Ar**F**), –155.4 (1F, t, *J* = 20.8 Hz, Ar**F**), –162.0 (2F, ddd, *J* = 22.0, 22.0, 7.8 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{10}H_9F_5O$ [M^+]: 240.0568, found: 240.0565.



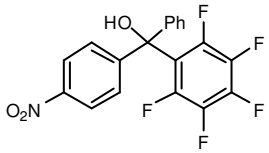
2,2-Dimethyl-1-pentafluorophenylpropan-1-ol (4s)

The title compound was prepared according to General Procedure C from trimethylacetaldehyde (109 μL, 1.00 mmol) for a reaction time of 3 h at –78 °C and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil (141 mg, 56%). R_f = 0.38 (10% EtOAc/hexane); IR (film) 3512 (OH), 2363, 1652, 1522, 1498, 1330, 1121, 1064, 990, 959 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.78 (1H, s, C**H**OH), 2.47 (1H, br, O**H**), 1.00 (9H, t, *J* = 1.5 Hz, ^{t}Bu); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 144.8 (2 x C, dm, *J* = 255.5 Hz), 140.2 (C, dm, *J* = 253.7 Hz), 137.4 (2 x C, dm, *J* = 253.0 Hz), 115.3 (C, t, *J* = 16.1 Hz), 75.6 (CH), 37.2 (C) 25.5 (3 x CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) δ –139.4 (2F, dd, *J* = 22.6, 7.4 Hz, Ar**F**), –155.4 (1F, t, *J* = 20.8 Hz, Ar**F**), –162.2 (2F, m, Ar**F**); *m/z*: No mass ion peaks observed under a range of mass spectroscopic techniques.



2-Hydroxy-2-pentafluorophenylpropionic acid ethyl ester (12b)

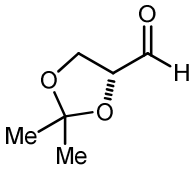
The title compound was prepared according to General Procedure C from ethyl pyruvate (111 μL, 1.00 mmol) for a reaction time of 23 h and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil (87 mg, 31%). R_f = 0.24 (10% EtOAc/hexanes); IR (film) 3484 (OH), 2988, 2923, 1743 (C=O), 1655, 1526, 1495, 1252, 1138, 988 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.34-4.25 (2H, m, C**H**$_2$CH$_3$), 4.08 (1H, br, O**H**), 1.91 (3H, t, *J* = 3.1 Hz, CC**H**$_3$), 1.27 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 174.3 (C), 145.7 (2 x C, dm, *J* = 251.0 Hz), 140.9 (C, dm, *J* = 255.5 Hz), 137.7 (2 x C, dm, *J* = 253.2 Hz), 116.0 (C, t, *J* = 12.4 Hz), 73.3 (C), 63.2 (CH_2), 26.2 (CH_3, t, *J* = 5.7 Hz), 13.8 (CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) δ –139.8 (2F, ddd, *J* = 19.8, 6.1, 3.1 Hz, Ar**F**), –154.1 (1F, t, *J* = 20.7 Hz, Ar**F**), –162.0 (2F, ddd, *J* = 20.7, 19.8, 6.1 Hz, Ar**F**); *m/z*: No mass ion peaks observed under a range of mass spectroscopic techniques.



(4-Nitrophenyl)(pentafluorophenyl)phenylmethanol (12c)

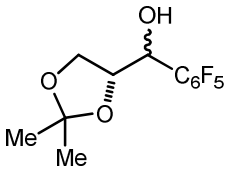
The title compound was prepared according to General Procedure B from 4-nitrobenzophenone (227 mg, 1.00 mmol) for a reaction time of

16 h, but with the following workup procedure: 1 mL of HCl (~ 1M in MeOH/H_2O) was added and the mixture was heated under reflux for 5 h. The solvent was removed *in vacuo* and the resulting mixture was partitioned between saturated aqueous $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/hexane) to gave a pale yellow oil (191 mg, 48%). R_f = 0.29 (10% EtOAc/hexanes); IR (film) 3538 (OH), 3063, 1650, 1606, 1522 (NO_2), 1487, 1349 (NO_2), 1112, 994, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.18 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.50 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.43-7.41 (3H, m, Ar**H**), 7.30-7.28 (2H, dd, *J* = 6.6, 3.0 Hz, Ar**H**), 3.81 (1H, t, *J* = 4.5 Hz, O**H**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 151.2 (C), 147.5 (C), 145.0 (2 x C, dm, *J* = 249.5 Hz), 143.1 (C), 141.0 (C, dm, *J* = 256.5 Hz), 138.0 (2 x C, dm, *J* = 254.4 Hz), 128.9 (CH), 128.8 (2 x CH), 128.1 (2 x CH), 126.4 (2 x CH), 123.2 (2 x CH), 119.8 (C, t, *J* = 11.1 Hz), 80.1 (C); ^{19}F NMR (235 MHz, $CDCl_3$) δ –136.4 (2F, ddd, *J* = 20.3, 5.6, 4.5 Hz, Ar**F**), –153.0 (1F, tt, *J* = 21.4, 2.8 Hz, Ar**F**), –160.7 (2F, ddd, *J* = 21.4, 20.3, 5.6 Hz, Ar**F**); HRMS (EI) Exact mass calcd for $C_{19}H_{10}F_5NO_3$ [M^+]: 395.0575, found: 395.0574.



(4*R*)-2,2-Dimethyl-1,3dioxolane-4-carbaldehyde (2u)[41]

The title compound was prepared according to a literature procedure.[41] To a suspension of silica-supported sodium periodate (6.0 g) in CH_2Cl_2 (15 mL), was added 1,2:5,6-di-*O*-isopropylidene-D-mannitol (0.79 g, 3 mmol) in CH_2Cl_2 (15 mL).The mixture was allowed to stur at room temoerature for 1 hour. The periodate was removed by filtration and washed with $CHCl_3$ (3 x 30 mL). The reaction mixture was concentrated *in vacuo* to give the named compound as a colourless oil (0.53 g, 68%), which was used without further purification. ^1H NMR (360 MHz, $CDCl_3$) δ 9.66 (1H, d, *J* = 1.8 Hz, O=C**H**), 4.34 (1H, ddd, *J* = 7.2, 4.7, 1.8 Hz, C**H**CHO), 4.12 (1H, dd, *J* = 13.3, 7.2 Hz, C$\mathbf{H}_2$), 4.06 (1H, dd, *J* = 13.3, 4.8 Hz, C$\mathbf{H}_2$), 1.44 (3H, s, CH_3), 1.37 (3H, s, CH_3).



[(4*R*)-2,2-Dimethyl-1,3-dioxolane-4-yl](pentafluorophenyl)methanol (4u)

The title compound was prepared according to General Procedure B from **2u** (130 mg, 1.00 mmol) for a reaction time of 16 h starting at −78 °C and warming gradually to room temperature, but with the following workup procedure: TBAF

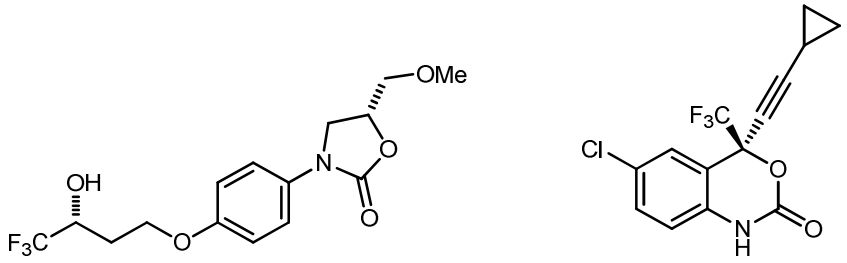
(1.0M in THF, 1 mL) was added and the mixture was stirred at room temperature for 90 minutes. Saturated $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc/hexane) to give a colourless oil (43 mg, 14%, 1.2:1 *dr*) Major diastereomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.91 (1H, d, *J* = 12.2 Hz, C**H**OH), 4.49-4.39 (1H, m, C**H**$_2$), 4.17 (1H, d, *J* = 3.6 Hz, O**H**), 4.12 (1H, dd, *J* = 10.4, 10.1 Hz, C**H**$_2$), 3.80 (1H, d, *J* = 5.4 Hz, C**H**), 1.39 (3H, s, C**H**$_3$), 1.31 (3H, s, C**H**$_3$); ^{19}F NMR (235 MHz, $CDCl_3$) δ –143.2 (2F, ddd, *J* = 22.3, 6.3, 5.4 Hz, Ar**F**), –154.6 (1F, tt, *J* = 20.0, 5.4 Hz, Ar**F**), –162.1 (2F, ddd, *J* = 22.3, 20.0, 6.3 Hz, Ar**F**).

Minor diastereomer: : ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.97 (1H, d, *J* = 9.4 Hz, C**H**OH), 4.49-4.39 (1H, m, C**H**$_2$), 4.17 (1H, d, *J* = 1.4 Hz, O**H**), 4.01 (1H, dd, *J* = 12.6, 9.4 Hz, C**H**$_2$), 3.76 (1H, d, *J* = 5.3 Hz, C**H**), 1.52 (3H, s, C**H**$_3$), 1.38 (3H, s, C**H**$_3$); ^{19}F NMR (235 MHz, $CDCl_3$) δ –142.1 (2F, ddd, *J* = 22.0, 6.9, 2.4 Hz, Ar**F**), –154.1 (1F, tt, *J* = 21.2, 2.4 Hz, Ar**F**), –162.1 (2F, ddd, *J* = 22.0, 21.2, 6.9 Hz, Ar**F**).

3. Enantioselective Synthesis of Fluoroalkylated Stereocentres

3.1 Introduction

With the exception of the fluorine atom itself, the trifluoromethyl group is the most common fluorine-containing functional group used in medicinal chemistry.[43] Some examples of commercial products containing trifluoromethyl stereocentres are given in **Scheme 3.1**. Therefore, general methods for the synthesis of chiral fluoroalkylated compounds are highly desirable.



Befloxatone
antidepressant

Efavirenz
anti-HIV

Scheme 3.1

There are complementary approaches to the enantioselective synthesis of chiral fluoroalkylated species: direct enantioselective fluoroalkylation, or the asymmetric elaboration of a prochiral fluoroalkylated molecule.

3.1.1 Direct Enantioselective Trifluoromethylation

In recent years, direct trifluoromethylation has become a rapidly growing field. The introduction of a trifluoromethyl group into a molecule differs from the introduction of single fluorine atoms, as it is a carbon–carbon bond-forming reaction. However, methods that are

applicable for the introduction of methyl groups are rarely compatible with the trifluoromethyl group. This makes direct trifluoromethylation a unique challenge.

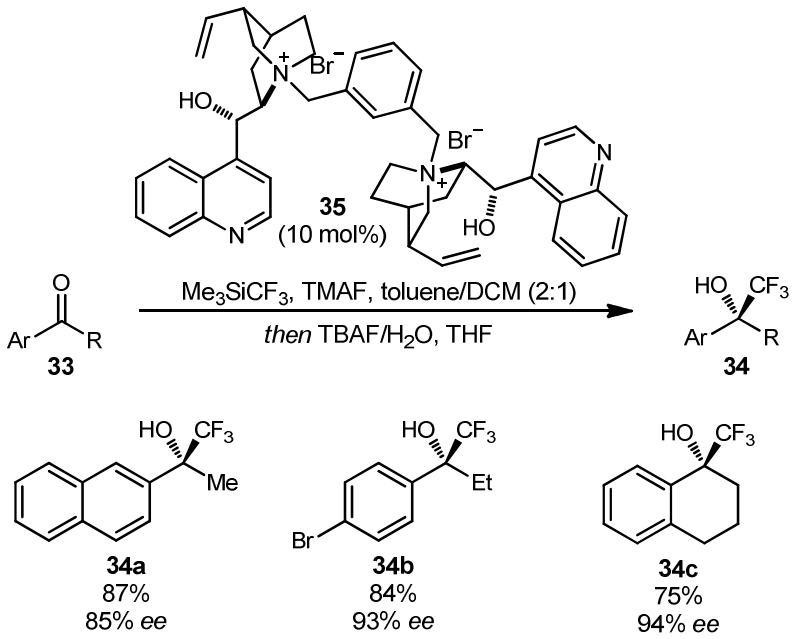
There are three broad categories of direct trifluoromethylation, each with its own difficulties. These are radical, electrophilic and nucleophilic trifluoromethylations. Direct nucleophilic trifluoromethylation is by far the most developed of these fields and it is in this area that the current literature on the development of asymmetric trifluoromethylation reactions is focused upon.

The trifluoromethyl anion is intrinsically unstable and readily undergoes α-elimination of fluoride to generate difluorocarbene. As a result, it is necessary to stabilise trifluoromethyl anion equivalents and the most common method for this is the use of a metal centre. In 1984, Ruppert reported the synthesis of (trifluoromethyl)trimethylsilane (**32**).[44] Five years later, the reagent was first used by Prakash to trifluoromethylate carbonyl compounds[45] and since then it has been used extensively in nucleophilic trifluoromethylation reactions.

Ruppert's reagent is used very regularly in trifluoromethylation reactions as a result of its stability, non-toxicity and relatively low cost. $TMSCF_3$ does not itself react with electrophiles. However, the silicon centre is highly susceptible to nucleophilic attack, giving rise to a pentavalent silicon complex, which can transfer the CF_3 group to a suitable electrophile. Other fluoroalkyl or fluoroaryl silane reagents can be used in the same manner to introduce fluorine-containing functional groups such as the pentafluoroethyl, heptafluoropropyl, or pentafluorophenyl (*vide supra*) groups.

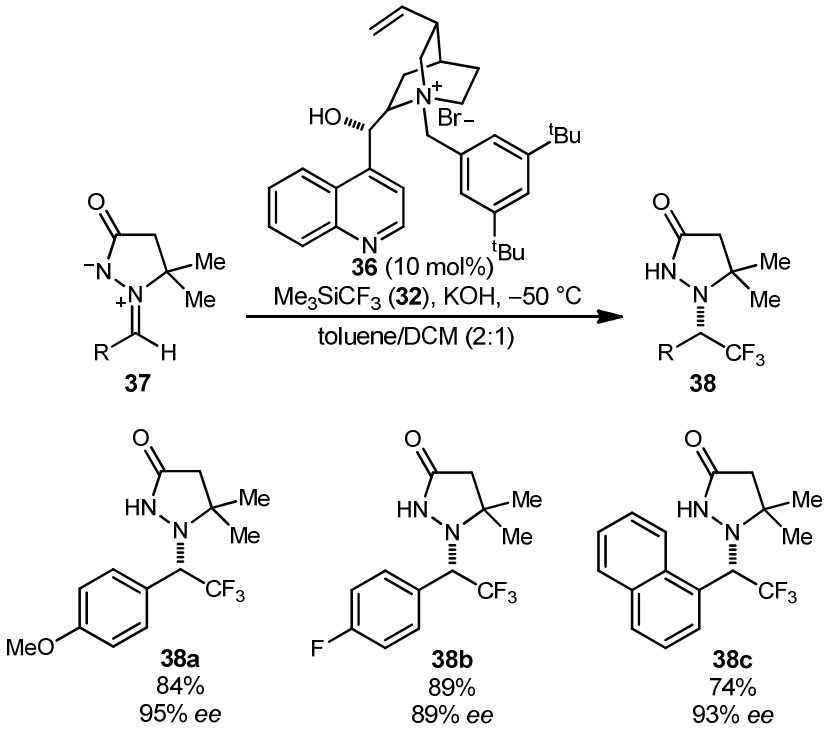
The mechanism for this reaction is shown in **Scheme 2.2** for the pentahalogenophenyl analogues. Examples of nucleophilic activators that have been employed with Ruppert's reagent in trifluoromethylation reactions are TBAF,[45] KO^tBu[45] and CsF.[46] Logically, the use of chiral activators for Ruppert's reagent would seem to be an excellent strategy for asymmetric nucleophilic trifluoromethylation. Indeed, there have been many reports of such an approach to the trifluoromethylation of carbonyls, with varying levels of success. One example which shows particular promise was reported by Shibata in 2007.[47] A chiral quaternary ammonium bromide is employed in conjunction with tetramethylammonium fluoride to synthesise trifluoromethyl alcohols from ketones (**Scheme 3.2**). Three substrates

are trifluoromethylated with *ee*s greater than 90% and there are a further 10 examples with enantiomeric excesses in the range of 85-89%.



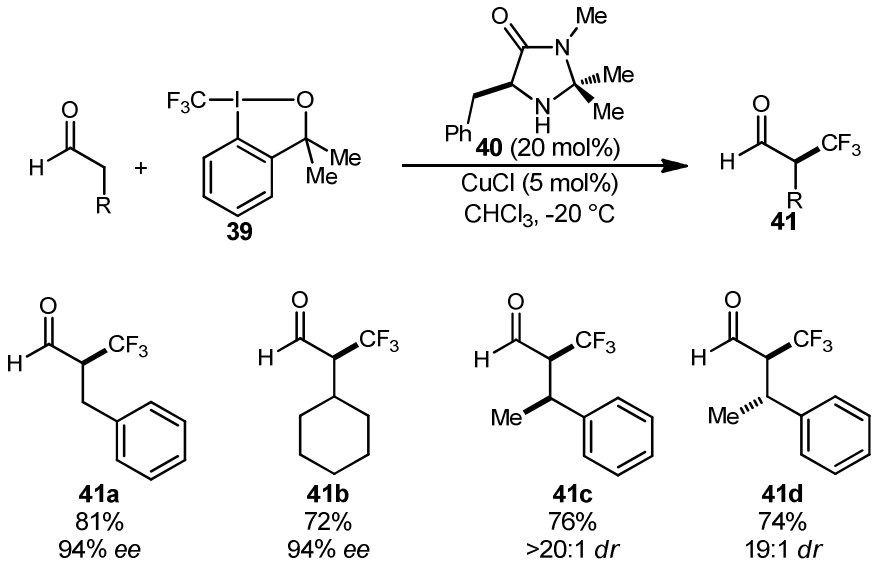
Scheme 3.2

This methodology has also been extended to the trifluoromethylation of azomethine imines in the first example of the enantioselective nucleophilic trifluoromethylation of C=N bonds.[48] The enantiomeric excesses are even higher than those obtained for alkyl aryl ketones with 10 examples showing an *ee* of greater than 90% (**Scheme 3.3**).



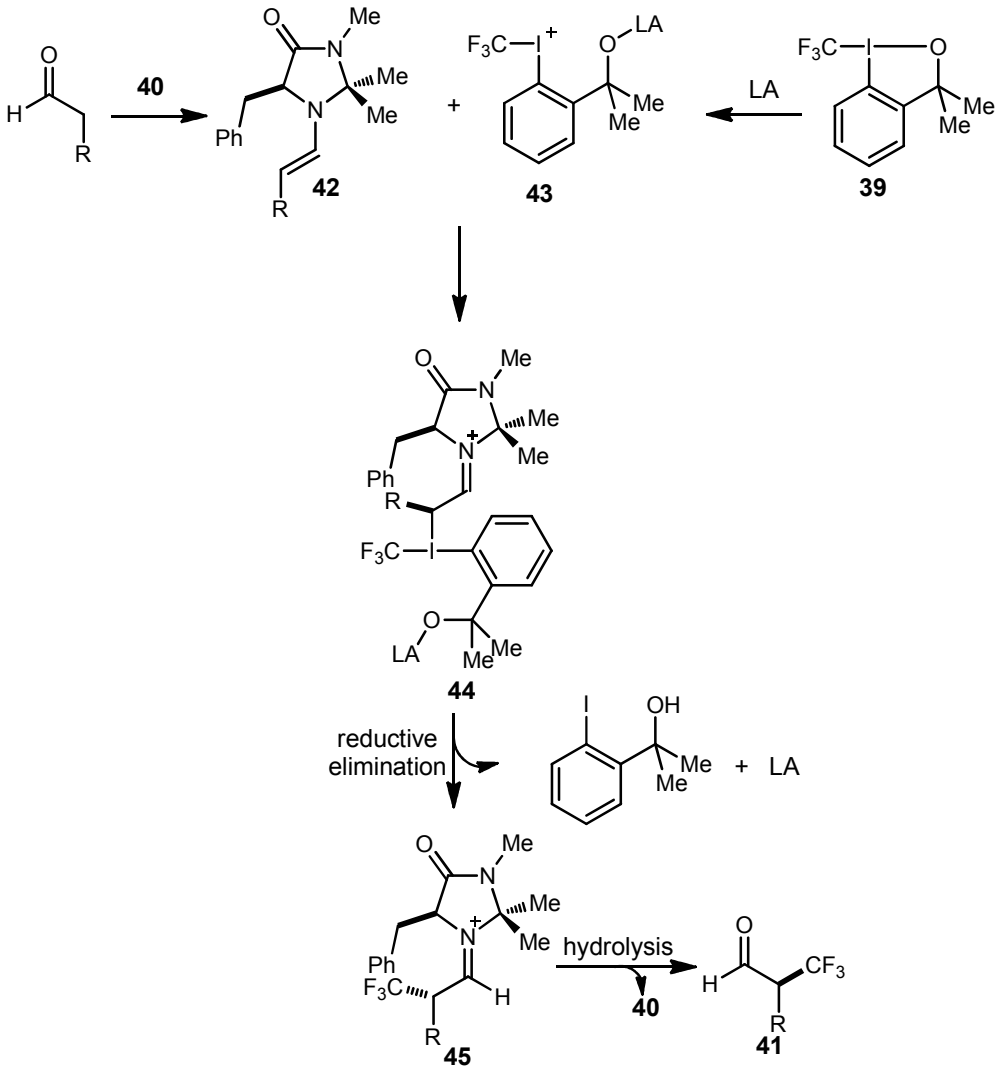
Scheme 3.3

Although much less common than nucleophilic examples, there have been reports of enantioselective electrophilic trifluoromethylations. Most of these gave very disappointing enantioselectivities and/or required expensive or non-commercial trifluoromethyl sources. By far the most impressive example to date of an enantioselective electrophilic trifluoromethylation is that published by Macmillan and co-workers in 2010.[49] This approach employs Togni's reagent (**39**), a hypervalent iodonic trifluoromethylation reagent, along with a Lewis acid and an organocatalyst to carry out the enantioselective α-trifluoromethylation of aldehydes. The reaction works well for a wide range of aldehyde substrates and the enantiomeric excesses of the products are all excellent (93-97%, **Scheme 3.4**).



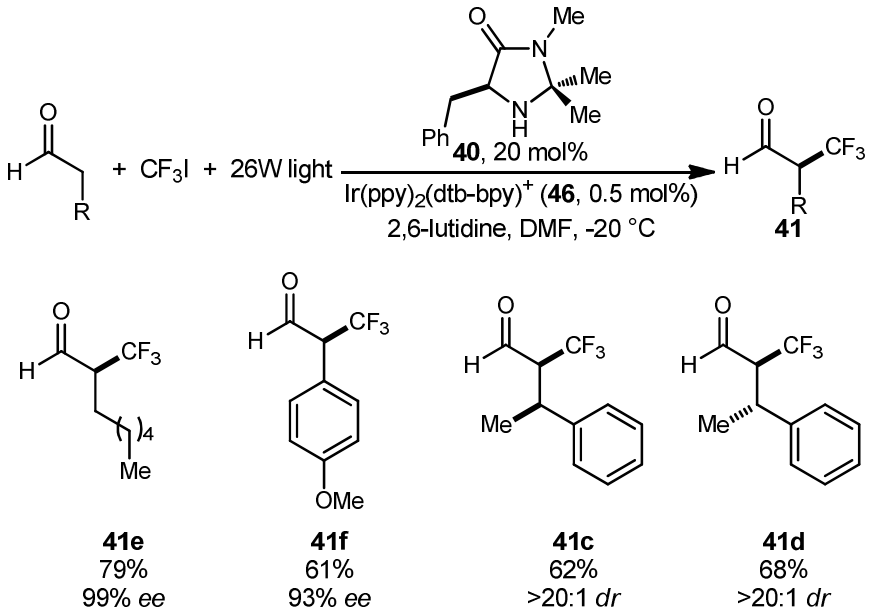
Scheme 3.4

The proposed mechanism for this reaction is given in **Scheme 3.5**. Togni's reagent undergoes Lewis acid-catalysed cleavage of the I–O bond to generate **43**, a highly electrophilic iodonium salt. Compound **43** will then react with the enamine species (**42**), generated by the condensation of the aldehyde substrate with the organocatalyst, from the least sterically hindered face, to form **44**. Reductive elimination at the iodine centre then generates the desired C–CF_3 bond with retention of stereochemistry. Hydrolysis of the iminium ion will regenerate the organocatalyst and produce a molecule of the trifluoromethylated product.



Scheme 3.5

The only example in the literature of an effective enantioselective radical trifluoromethylation also comes from the MacMillan group.[50] In 2009, they published their first report of the enantioselective *α*-trifluoromethylation of aldehydes using photoredox organocatalysis (**Scheme 3.6**). An organocatalyst is used as above to generate a chiral enamine, which is selectively attacked at the least hindered face by a trifluoromethyl radical. The trifluoromethyl radical is generated through the use of visible light in conjuction with $Ir(ppy)_2(dtb\text{-}bpy)^+$ (**46**). Again, the conditions are tolerant of a range of functionalities and *ee*s are excellent.



Scheme 3.6

Despite the significant level of interest in enantioselective trifluoromethylation reactions, there is still a lack of general methods that consistently give high yields and *ee* values. There are also limited motifs for which the above synthetic approaches can be used. For example, the direct asymmetric trifluoromethylation approach has not been used to synthesise molecules with all-carbon quaternary stereocentres. One possible method for the generation of all-carbon stereocentres is through a conjugate addition reaction. However, the conjugate addition of Ruppert's reagent has only been described in limited cases for particularly reactive substrates[35,51] and there has never been a report of an enantioselective version.

In these cases, the most commonly used method is the asymmetric elaboration of prochiral trifluoromethyl alkenes. Reviews on the reactions of prochiral trifluoromethyl substrates have been published[52] and, as such, we will limit ourselves here to the most relevant substrates to this work: *β*-fluoroalkyl-*α*,*β*-unsaturated carbonyls.

3.1.2 Asymmetric Elaboration of *β*-Fluoroalkyl-*α*,*β*-Unsaturated Carbonyl Compounds

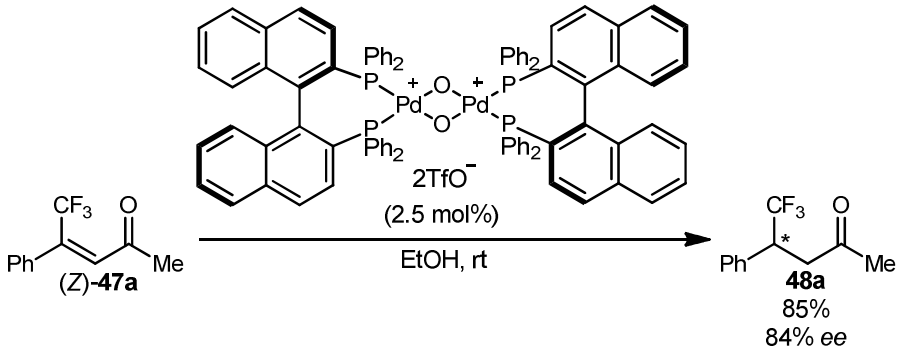
The great utility of *α*,*β*-unsaturated carbonyl compounds is due to presence of two reactive sites. Although this can cause problems initially due to the requirement for careful control of

regiochemistry, it can allow for simple further elaboration of the molecule leading to a rapid increase in complexity. The introduction of a trifluoromethyl substituent into the β-position of such substrates allows for the asymmetric synthesis of a fluorinated stereocentre through conjugate addition or the synthesis of a chiral fluoroalkylated allylic alcohol through a 1,2-addition.

There are several examples of asymmetric reactions on β-trifluoromethyl-α,β-unsaturated carbonyl compounds.

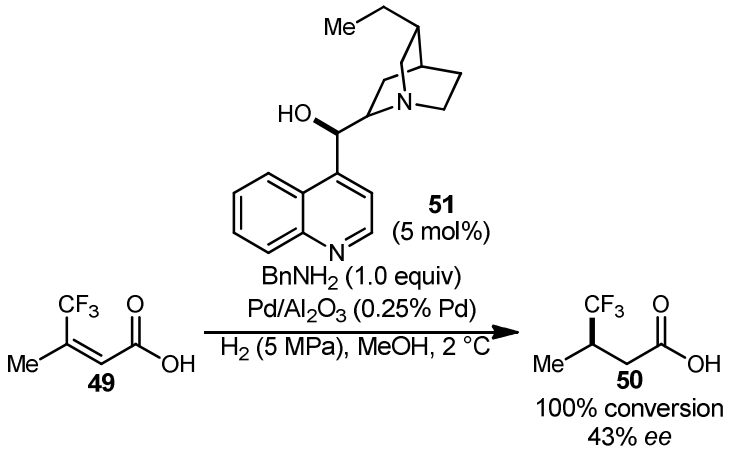
3.1.2.1 Asymmetric Reduction of β-Trifluoromethyl-α,β-Unsaturated Carbonyl Compounds

In 2006, the group of Sodeoka described an asymmetric palladium-catalysed conjugate reduction of enones.[53] One of the examples from this publication is the reduction of (*Z*)-**47a**, a β-trifluoromethyl enone to give **48a** as product in 85% yield with a good 84% enantiomeric excess (**Equation 3.1**). The reaction proceeds through the generation of Pd-H from ethanol via a β-hydride elimination.



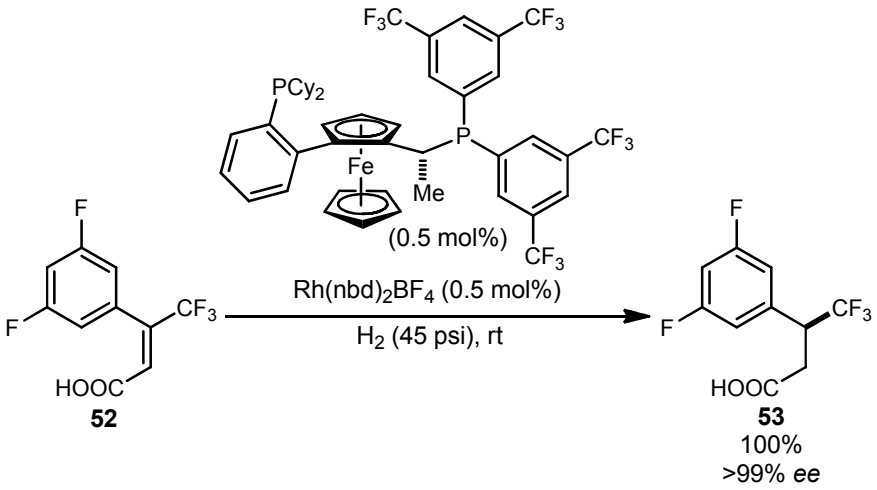
Equation 3.1

Szőllősi reported attempts to carry out an asymmetric palladium-catalysed conjugate reduction of fluorinated α,β-unsaturated carboxylic acids.[54] Unfortunately, although these substrates were found to be reactive under a range of conditions, the enantioselectivity remained low (**Equation 3.2**). The reaction was also found to lack generality, as application to another substrate gave barely any enantioselectivity at all.



Equation 3.2

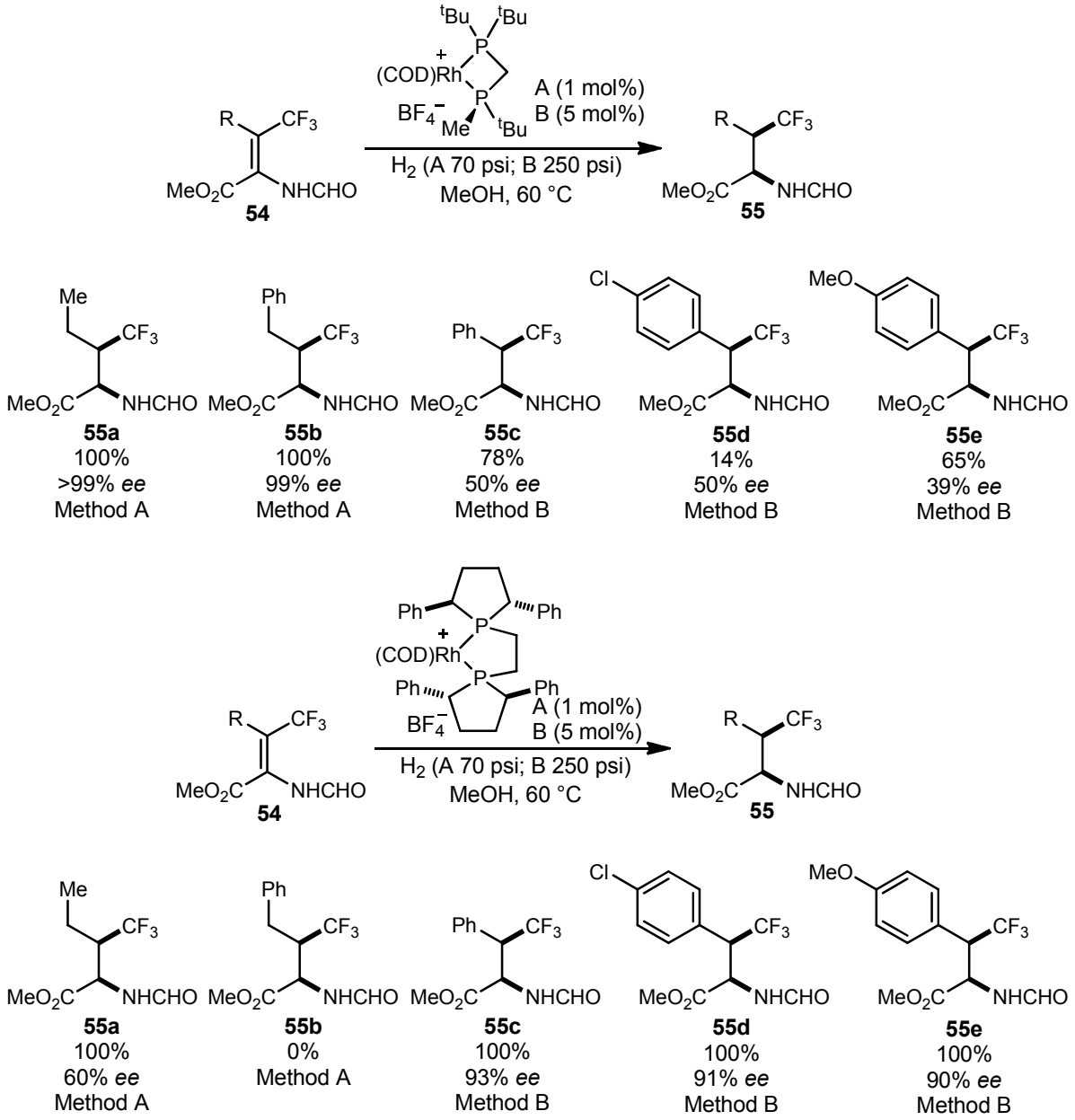
An improved result was disclosed by Alimardanov and co-workers in the following year.[55] Their catalyst system used rhodium in conjunction with a chiral Walphos ligand to give the desired product in quantitative yield with an enantiomeric excess of >99%. However, as this reaction was developed as part of a process-scale synthesis, there is only one substrate example in this publication (**Equation 3.3**).



Equation 3.3

Another rhodium-catalysed reduction was reported by Benhaim and co-workers.[56] In this case, the substrates were tetrasubstituted β-trifluoromethyl-α-dehydroamino esters. The effect of the ligand employed was found to differ from substrate to substrate. The optimum ligand found for substrates with an aryl group attached directly to the double bond (Ph-BPE) was different from that required when this was not the case (TCFP). As such, there were two

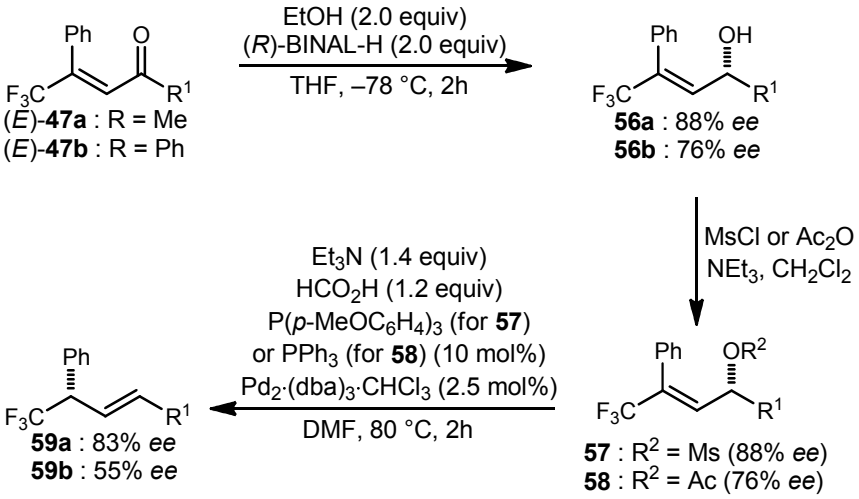
different sets of optimised conditions employed to obtain high yields and excellent enantiomeric excesses for all substrates (**Scheme 3.7**).



Scheme 3.7

Konno and co-workers have described the enantioselective synthesis of compounds with an allylic trifluoromethyl stereocentre starting from *β*-trifluoromethyl-*α*,*β*-unsaturated ketones.[57] Their approach commenced with the asymmetric reduction of the carbonyl moiety, followed by mesylation or acetylation of the product thus formed (**56**) to give a leaving group. The optically active mesyl or acetyl compounds (**57** and **58**) were then subjected to a palladium-catalysed formate reduction to give the corresponding product, **59 (Scheme 3.8)**. The initial

reduction was carried out using Noyori's BINAL-H reagent. For the two examples described, enantiomeric excesses of 88% and 76% were obtained. No loss of *ee* occurred during the mesylation or acetylation step. However, the palladium-catalysed formate reduction step did result in a significant decrease in *ee* for substrate **59b**.



Scheme 3.8

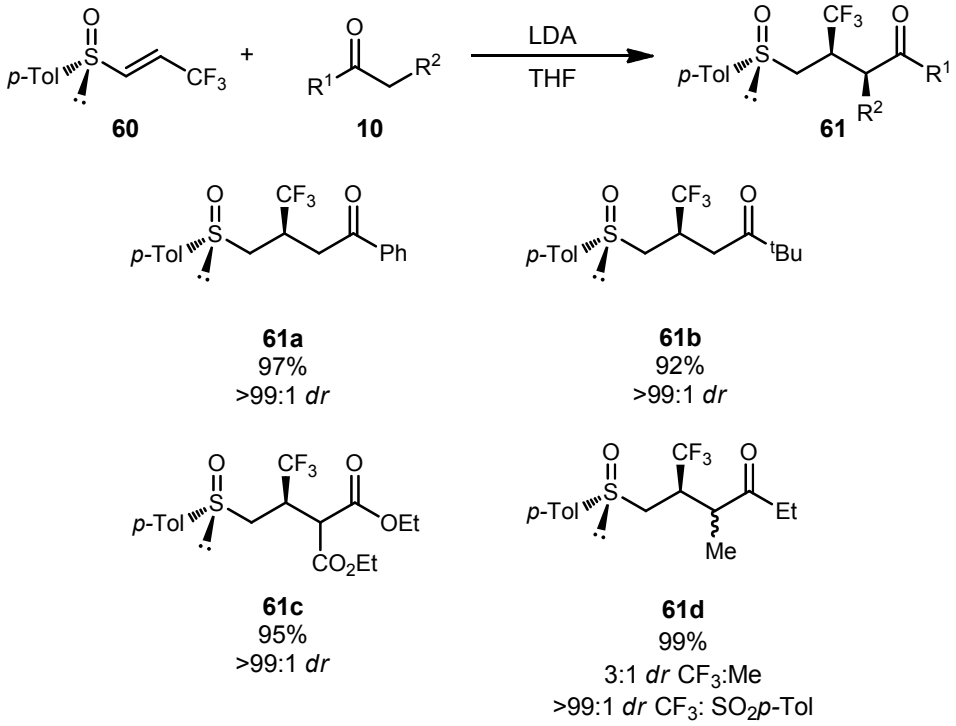
Reductions are not the only type of asymmetric reaction that have been reported for these substrates. Conjugate additions of various carbon nucleophiles have also been described.

3.1.2.2 Enantio- and Diastereoselective Conjugate Additions to *β*-Trifluoromethyl-*α*,*β*-Unsaturated Carbonyl Compounds and Sulfoxides

As we have seen, several enantioselective reductions of *β*-trifluoromethyl *α*,*β*-unsaturated carbonyl compounds exist. In contrast, the vast majority of the conjugate addition of carbon nucleophiles to these substrates that give chiral products are carried out diastereoselectively. This can be through the use of a chiral auxiliary or by reaction with an enantiomerically pure nucleophile.

Similarly to unsaturated carbonyl compounds, unsaturated sulfoxides, sulfones and sulfonamides make excellent substrates for conjugate addition reactions. An additional benefit to using such compounds is that sulfoxides can be chiral and, as such, diastereoselective reactions can be carried out on these substrates to generate trifluoromethyl

stereocentres stereoselectively. Ishikawa has reported the Michael reaction of 3,3,3-trifluoro-1-propenyl phenyl sulfoxide with a range of enolates.[58] The diastereoselectivities were very high in cases when the enolate was derived from a methyl ketone (**Scheme 3.9**). The diastereoselectivity of this reaction is explained by an 8-membered ring transition state in which the *p*-Tol group occupies a pseudo-equatorial position, thus decreasing the steric clash with R^1 (**Figure 3.1**). However, control over the relative positioning of the trifluoromethyl stereocentre and the additional stereocentre formed when $R^2 \neq H$ was much poorer. This is likely to be due to poor selectivity in enolate formation from **10**. The major product is that which comes from the *Z*-enolate (**Figure 3.1**).



Scheme 3.9 [a]NaH used in place of LDA.

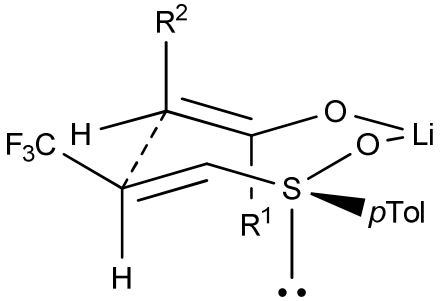
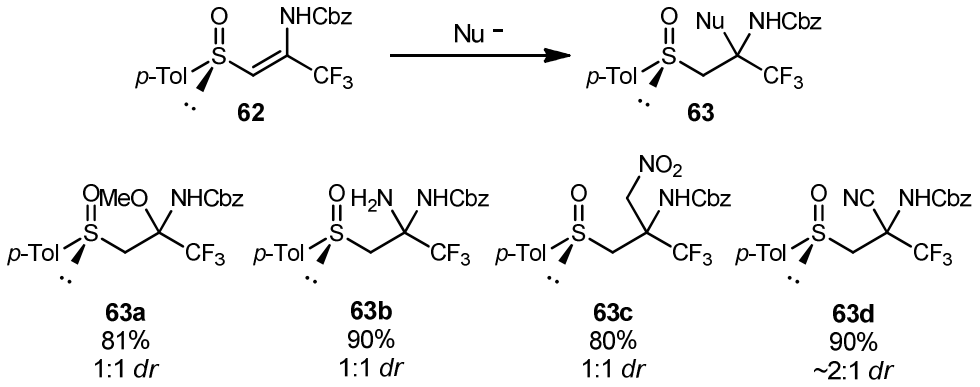


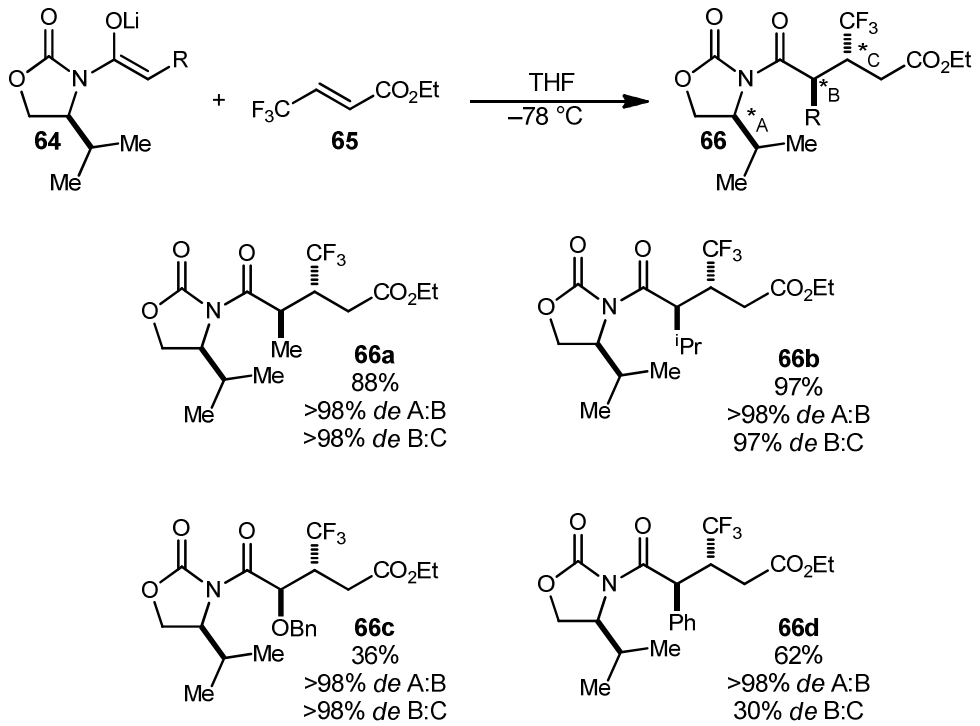
Figure 3.1

The group of Bravo have shown that α-(fluoroalkyl)-β-sulfinylenamines can undergo reaction with a range of nitrogen, oxygen or carbon-based nucleophiles.[59] Unfortunately, the measured diastereoselectivities were 1:1 for all examples (**Scheme 3.10**). The reaction of these substrates with sulfur nucleophiles, such as thiophenol, did not give the desired product; reduction of the sulfoxide group to the sulfide was observed. In a further publication by the same authors, the introduction of a CN nucleophile (**63d**) was also shown to work well, although again, the diastereoselectivity was poor.[60]



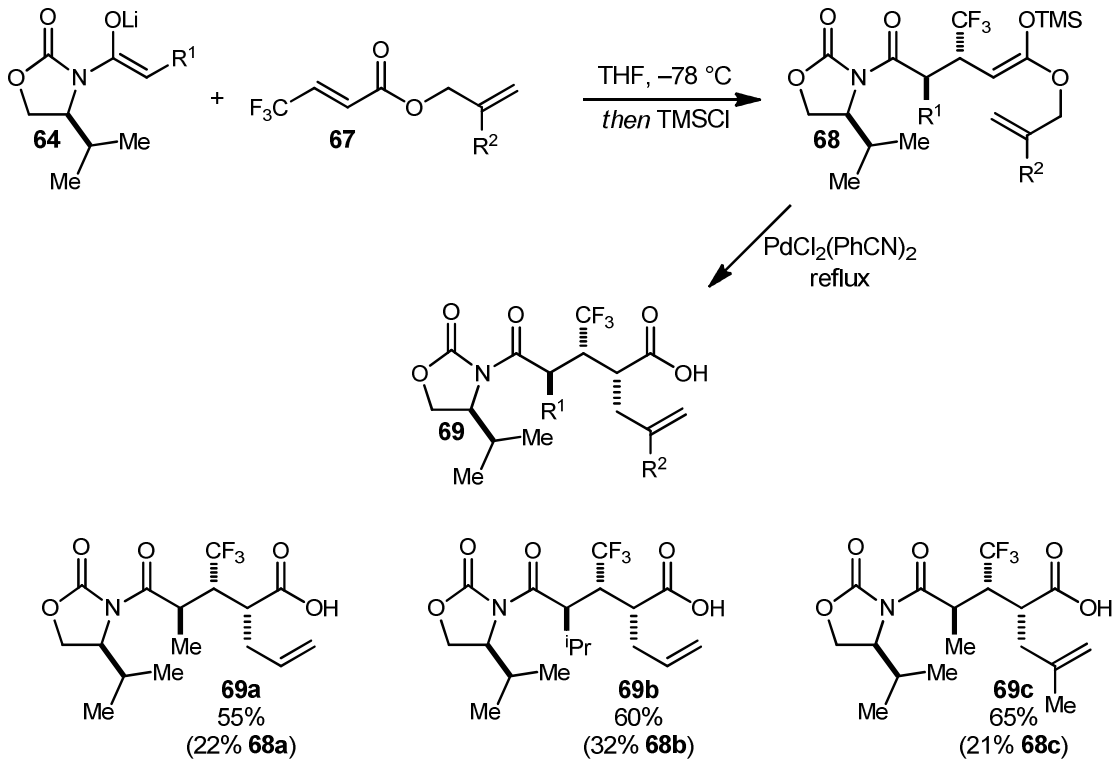
Scheme 3.10

Better selectivity is often observed when α,β-unsaturated carbonyl compounds are used. In particular, several diastereoselective or enantioselective conjugate additions to 4,4,4-trifluorocrotonate substrates and their derivatives have been reported. The first example was described by Yamazaki and co-workers in 1995.[61] Two stereocentres (one of which bears a trifluoromethyl substituent) could be created by the conjugate addition of chiral oxazolidinone-containing enolates to ethyl 4,4,4-trifluorocrotonate, often with excellent diastereoselectivities (**Scheme 3.11**).



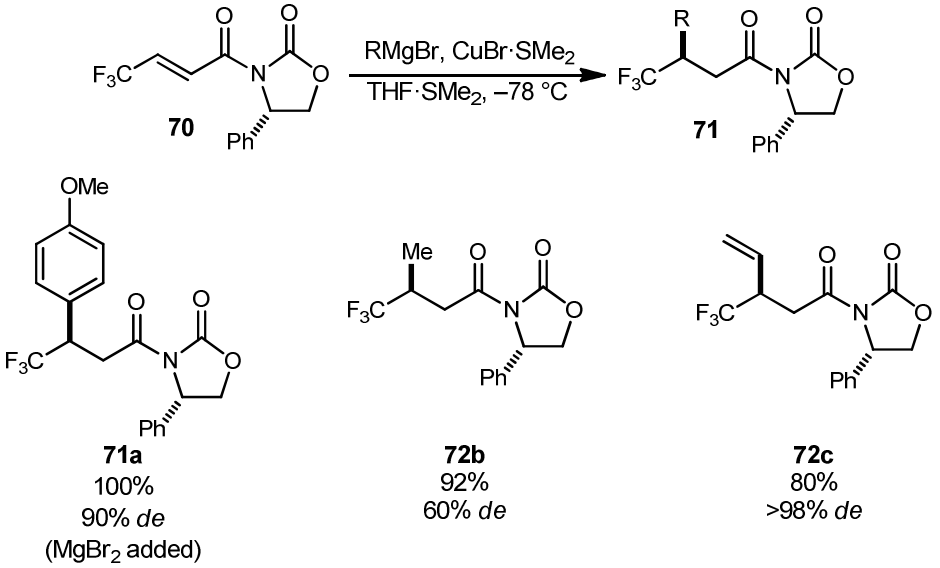
Scheme 3.11

A third stereocentre could be generated if the ester employed was changed from an ethyl to an allylic group.[62] In a one-pot procedure, the conjugate addition reaction was followed by the addition of TMSCl to generate ketene silyl acetal, **68**, which underwent an Ireland-Claisen rearrangement to give **69** (**Scheme 3.12**). Addition of $PdCl_2(PhCN)_2$ at this point prevented the generation of unwanted side-products. The product was obtained selectively as a single diastereomer, although variable amounts of the ester formed after the initial conjugate addition (**68**) were also isolated.



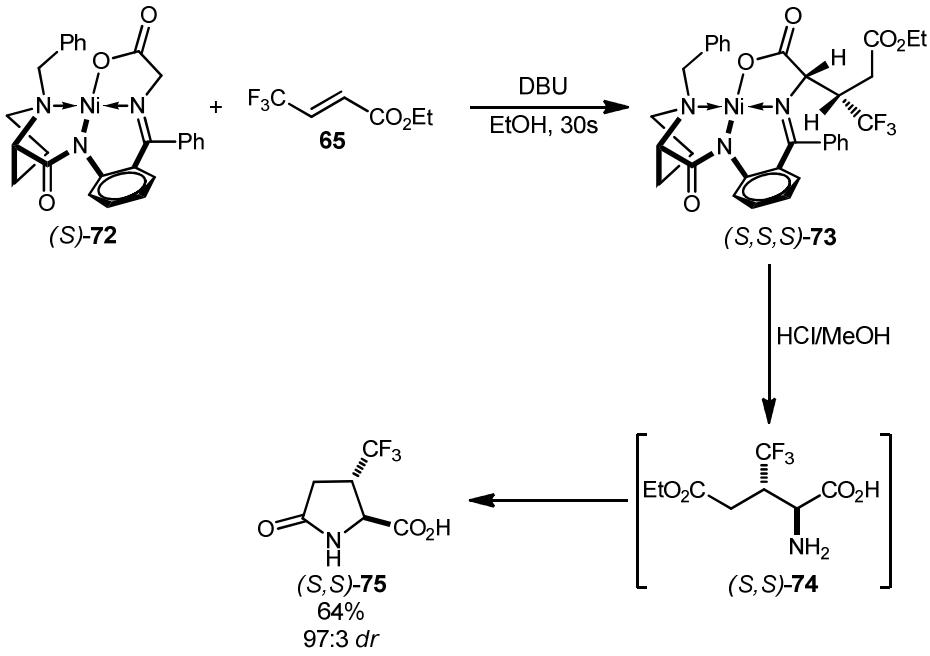
Scheme 3.12

The same group have also reported the reaction of chiral 4,4,4-trifluorocrotonimide substrates with organocopper reagents.[63] Excellent yields were obtained for a range of nucleophiles, although the diastereomeric excesses were variable (**Scheme 3.13**). In some cases, the addition of stoichiometric quantities of $MgBr_2$ was found to improve the selectivity.



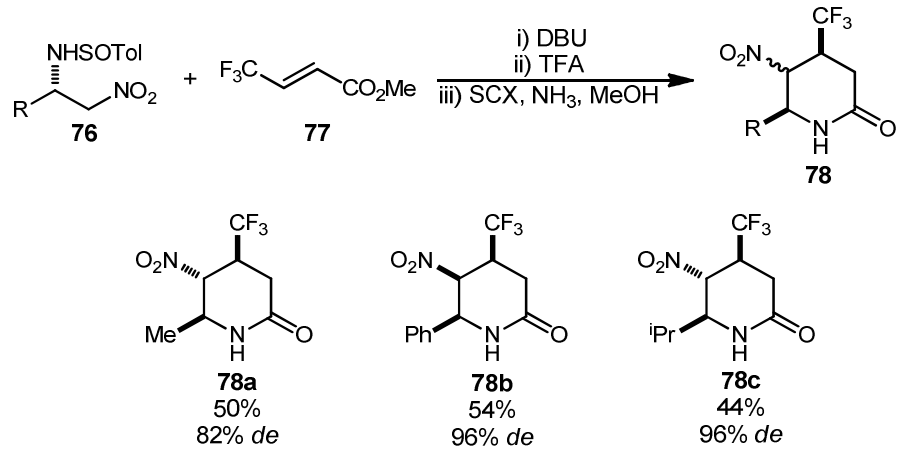
Scheme 3.13

The conjugate addition of a Ni(II) complex of a chiral Schiff base (made from glycine and a chiral benzophenone) to ethyl 4,4,4-trifluorocrotonate has also been reported (**Scheme 3.14**).[64] Interestingly, if the reaction was halted after 30 seconds, the isolated yield obtained was only 64%, but the diastereomeric ratio was excellent (97:3), whereas after 23 hours reaction time, the isolated yield increased to 97%, but the diastereomeric ratio became much poorer (81:19). This suggested that the reaction was reversible and the amount of the thermodynamic product formed increased as reaction times were prolonged.



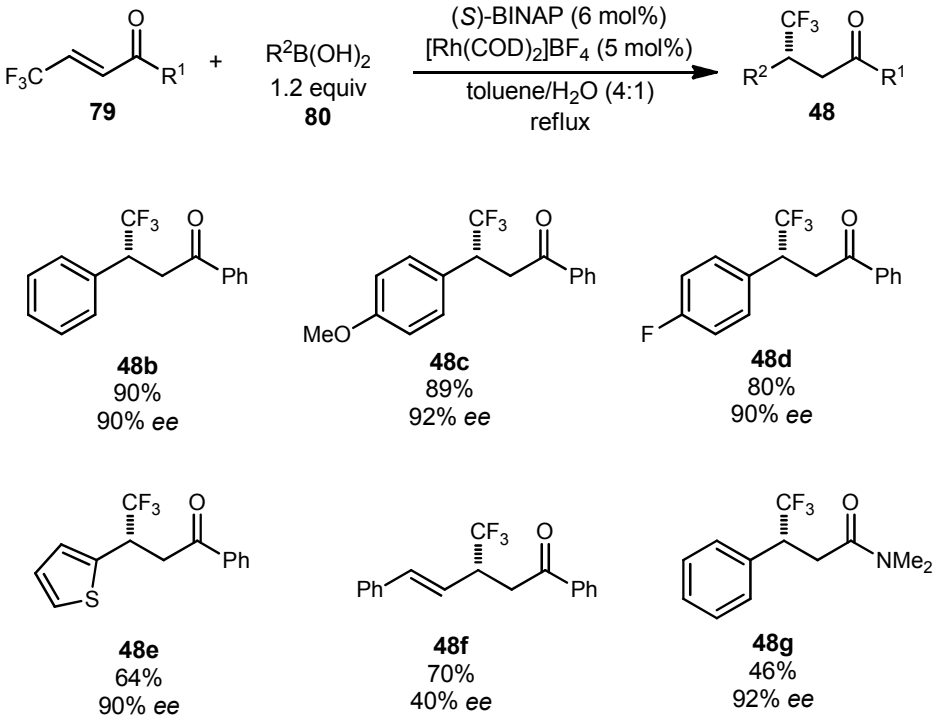
Scheme 3.14

Another set of nucleophiles that have been reported in the diastereoselective conjugate additions of chiral compounds to 4,4,4-trifluorocrotonates, are *N*-sulfinyl nitroamines.[65] After the conjugate addition, the sulfinyl group was removed with TFA, followed by purification by chromatography using SCX ion exchange resin. The desired nitropiperidone products are obtained in moderate yields and high *de*s (**Scheme 3.15**).



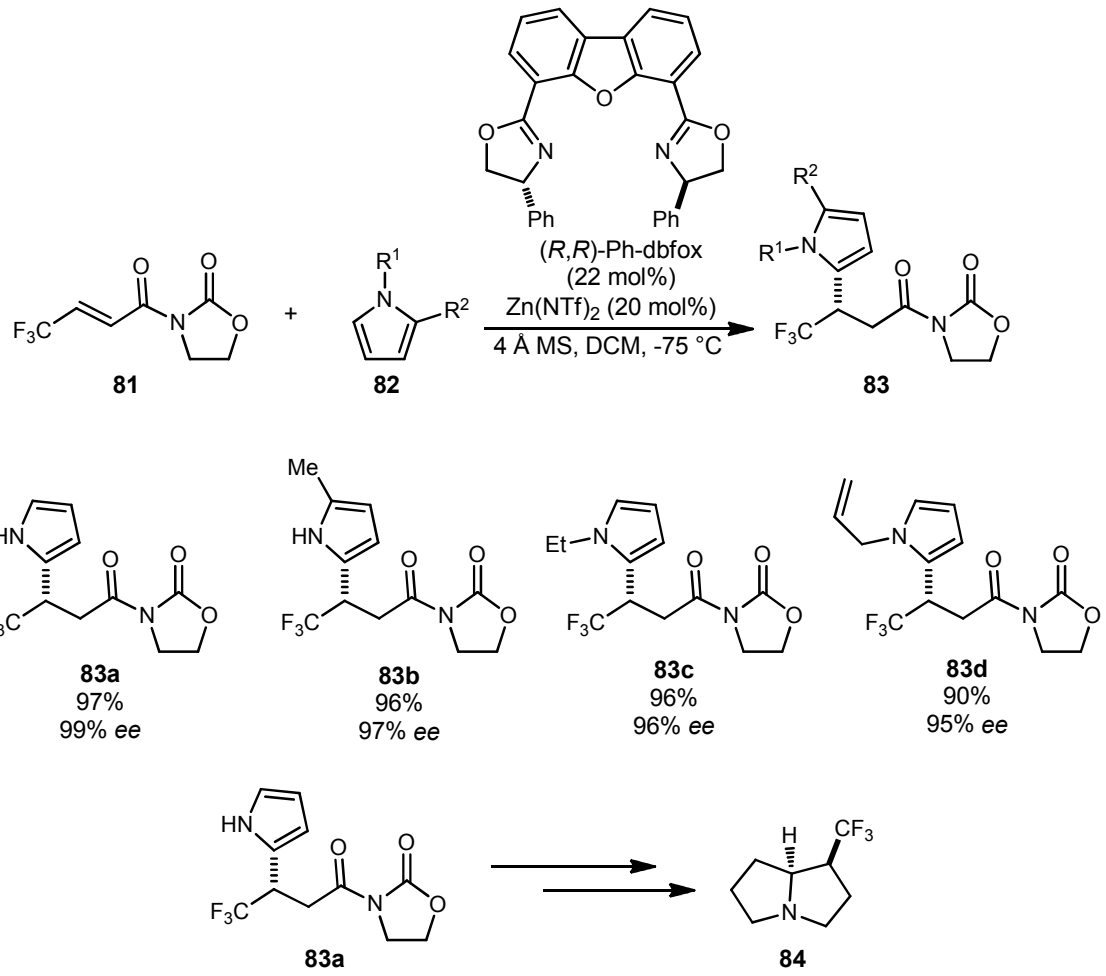
Scheme 3.15

All of the conjugate additions described thus far have been diastereoselective reactions of chiral molecules. However, the group of Konno have described the enantioselective rhodium-catalysed arylation and alkenylation of *β*-trifluoromethyl-*α*,*β*-unsaturated carbonyl compounds with boronic acids.[66] Excellent yields and enantioselectivities were obtained for a range of aryl boronic acids, although reaction with alkenylboronic acids gave somewhat lower *ee* values (**Scheme 3.16**). The methodology was also successfully extended to an unsaturated amide (**48g**).



Scheme 3.16

Another example of an enantioselective conjugate addition in which β-trifluoromethyl-α,β-unsaturated compounds have been reported is the Friedel-Crafts reaction. In 2010, Shibata described the enantioselective reaction of pyrroles with a β-trifluoromethyl acrylate under chiral Lewis acid catalysis (**Scheme 3.17**).[67] Yields and enantioselectivities were excellent and the utility of the products was demonstrated in the synthesis of trifluorinated heliotridane, **84**.



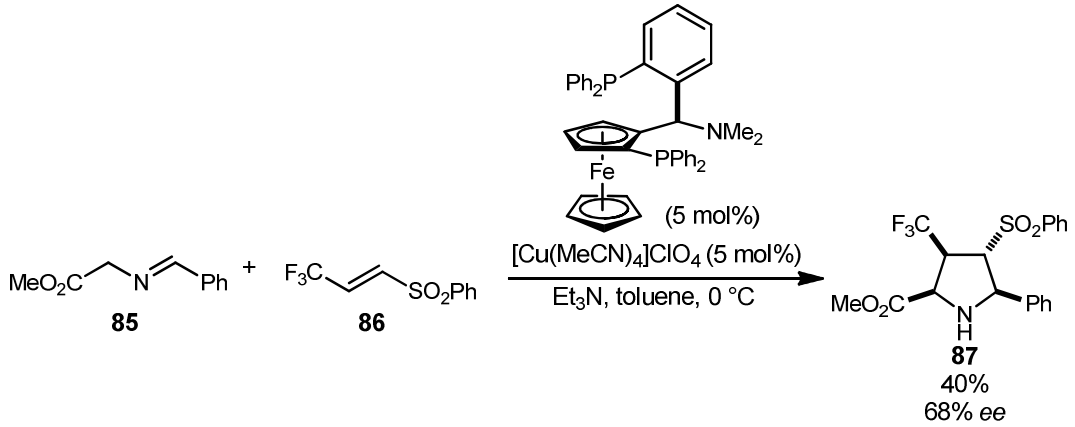
Scheme 3.17

The above reactions show that conjugate addition to fluoroalkylated unsaturated carbonyl compounds can be an effective approach to the synthesis of chiral fluorinated molecules. However, there are still many unexplored possibilities for these unsaturated substrates, such as the enantioselective synthesis of quaternary stereocentres or reactions that do not require chiral auxiliaries to give high *ee*s.

3.1.2.3 Asymmetric Cycloadditions of *β*-Trifluoromethyl-*α*,*β*-Unsaturated Sulfones and Nitroalkenes

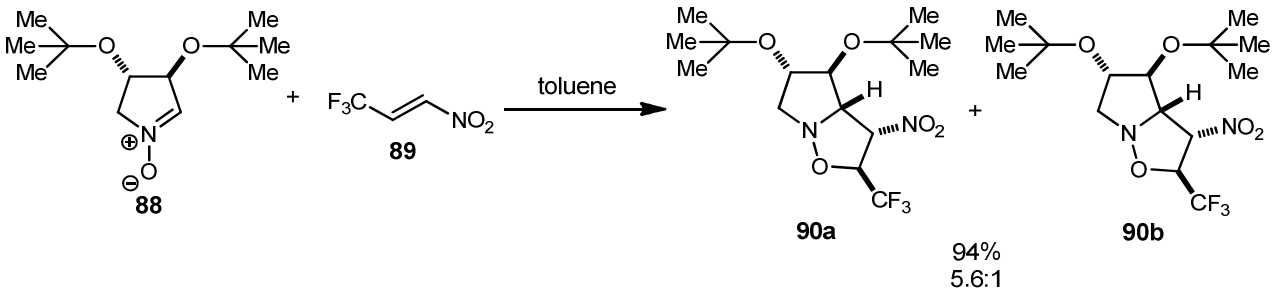
Another class of reactions that has been applied to *β*-trifluoromethyl-*α*,*β*-unsaturated carbonyl compounds to selectively give a trifluoromethyl-bearing stereocentre is the cycloaddition reaction.

The first such example was revealed by Carretero in 2007.[68] A *β*-trifluoromethyl vinyl sulfone reacted with an azomethine ylid in a 1,3-dipolar cycloaddition reaction under copper (I)-Taniaphos catalysis to give pyrrolidine **87** in moderate yield and enantiomeric excess (**Equation 3.4**).



Equation 3.4

Another 1,3-dipolar cycloaddition has been reported by Zanda.[69] Here, the reaction of a *β*-trifluoromethyl nitroalkene with a chiral nitrone gave trifluoromethylated isoxazolidines in a good 70% *de* (**Equation 3.5**).



Equation 3.5

Cycloadditions on unsaturated trifluoromethylated substrates have been shown as a method for the synthesis of chiral fluorinated materials by which several stereocentres can be controlled at once.

Although a number of enantioselective reactions have been carried out on β-trifluoromethyl α,β-unsaturated compounds, there is still plenty of scope for new methodology employing these substrates to give chiral trifluoromethylated products. For example, the synthesis of quaternary stereocentres through conjugate addition or the development of more general conditions for enantioselective reactions.

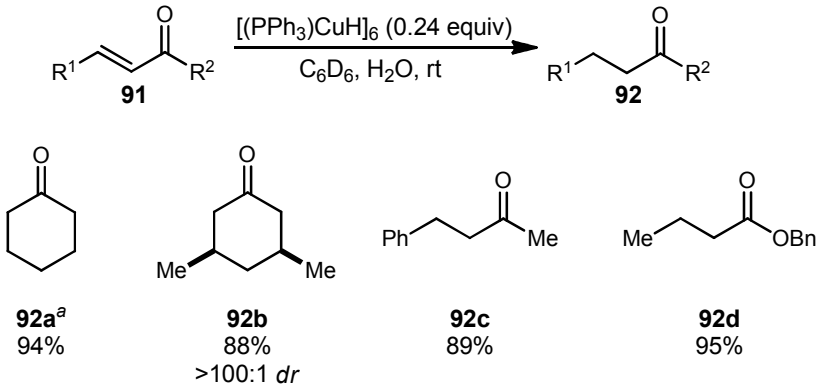
4. Copper-Hydride Reductions of *β*-Fluoroalkyl-*α*,*β*-Unsaturated Carbonyl Compounds

4.1. Introduction

The enantioselective formation of C-H bonds can be achieved through conjugate reductions. CuH is a mild source of hydride, which has shown versatility in highly regioselective and enantioselective conjugate reductions of *α*,*β*-unsaturated acceptors. Reviews of copper-catalysed reductions have been published.[70]

4.1.1 Conjugate CuH Reductions of *α*,*β*-Unsaturated Carbonyl Compounds

The most significant development in the field of CuH reduction chemistry was the discovery of the synthetic potential of Stryker's reagent in 1988.[71] Stryker's reagent is $[(PPh_3)CuH]_6$, a hexamer in which the Cu-H species is stabilised by phosphine ligands. There are several different reported methods for the synthesis of the reagent, but, in general, the rigorous exclusion of air is necessary and Stryker's reagent must be stored under inert conditions. **Scheme 4.1** illustrates the effectiveness of Stryker's reagent in the selective reduction of *α*,*β*-unsaturated carbonyl compounds.

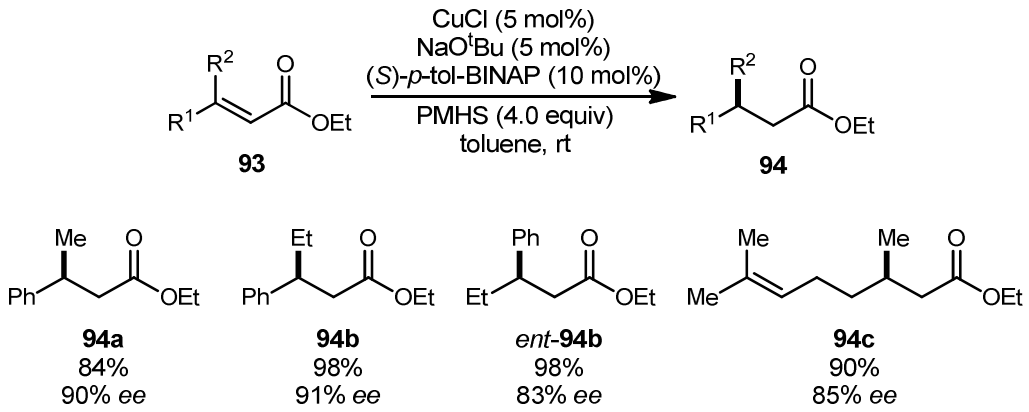


Scheme 4.1 [a]0.16 equiv Stryker's reagent used.

Although Stryker's reagent was originally reported as a stoichiometric reductant, possibilities for its employment in much more atom-economic catalytic processes were realised very early.[72] Stryker reports that the reaction of 2-cyclohexen-1-one with a substoichiometric quantity of $[(PPh_3)CuH]_6$ in benzene or toluene under 80 psi of hydrogen resulted in slow conversion to cyclohexanone as the sole product. They also describe the *in-situ* generation of CuH by stirring CuO^tBu and PPh_3 in toluene. At a hydrogen pressure of 200 psi, the reaction occurred more rapidly, but over-reduction to cyclohexanol was observed.

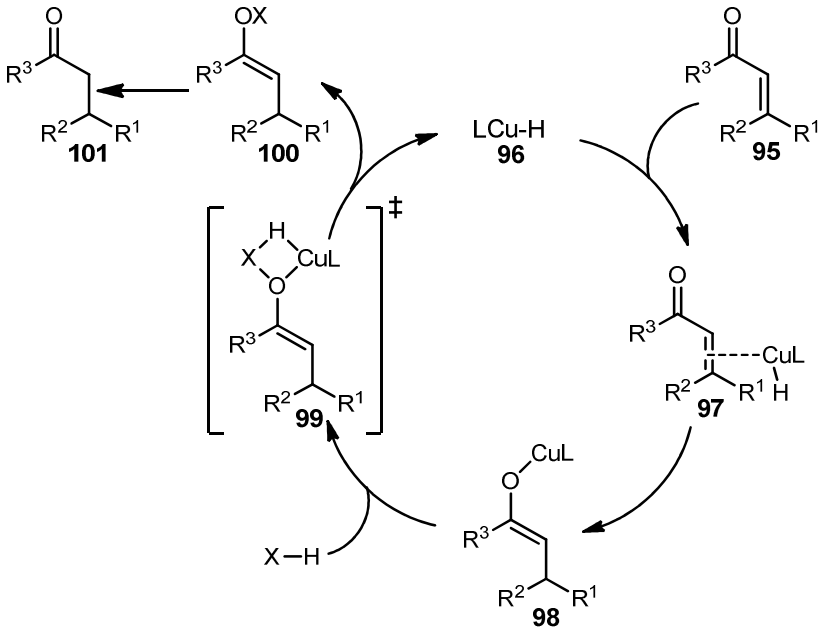
The extreme air-sensitivity of CuO^tBu is a major disadvantage of the system. $Cu(OAc)_2 \cdot H_2O$ has been found to act as a convenient alternative.[73] Another improvement in recent years has been the development of silanes as a source of stoichiometric hydride. Silanes are generally inexpensive and environmentally benign and several have been reported in CuH reductions; the most popular being polymethylhydrosiloxane (PMHS), tetramethyldisiloxane (TMDS), Fleming's silane ($PhMe_2SiH$) and phenylsilane.

The reductions can be made enantioselective if the triphenylphosphine ligands are replaced with chiral non-racemic bisphosphines. The earliest asymmetric reports came from the group of Buchwald. In 1999, the group reported the enantioselective conjugate reduction of *α,β*-unsaturated esters in excellent yields and enantiomeric excesses employing PMHS as the hydride source and *p*-tol-BINAP as the ligand (**Scheme 4.2**).[74] Two equivalents of ligand per metal centre were used as this was shown to give higher *ee*s, although experiments employing *p*-tol-BINAP ligands of different enantiomeric purities showed that the active catalyst complex contains ligand and metal in a 1:1 ratio.



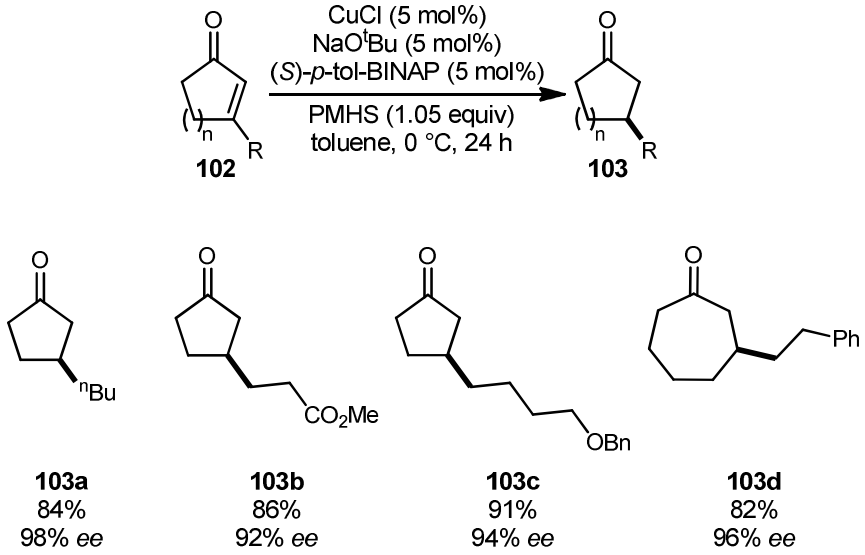
Scheme 4.2

The proposed catalytic cycle for the conjugate reductions is given in **Scheme 4.3**.[70(a)] The copper hydride species **96** generated *in-situ* reacts with a molecule of the substrate to form a π-complex **97**. The hydride is then delivered to the *β*-carbon to give the copper enolate **98**, which undergoes metathesis with the stoichiometric source of hydride via transition state **99** to regenerate a molecule of CuH and one of the desired product **101**.



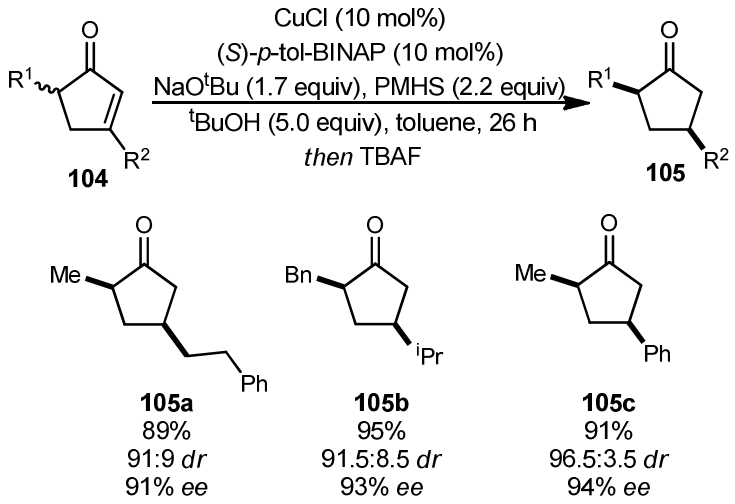
Scheme 4.3

In 2000, the same group reported the enantioselective reduction of *β*-alkyl cyclopentanones under the same conditions (**Scheme 4.4**).[75] Again, enantiomeric excesses were excellent. The amount of PMHS used had to be restricted to 1.05 equivalents as any excess led to over-reduction to the corresponding alcohol.

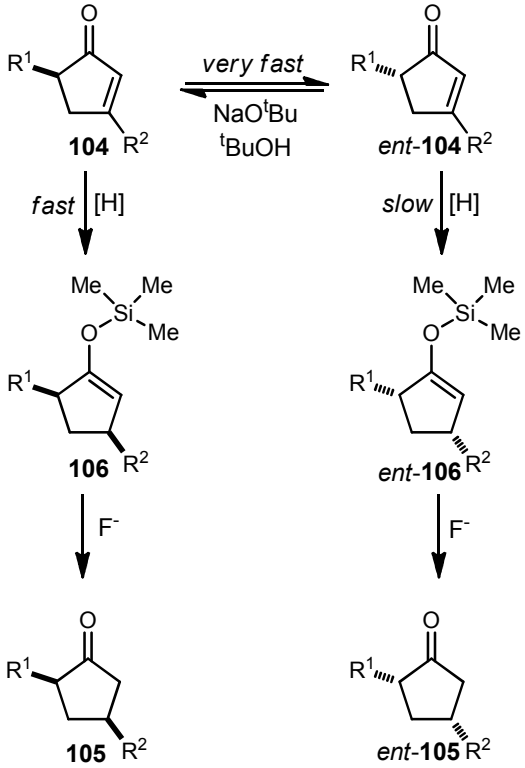


Scheme 4.4

This chemistry has also found application in the dynamic kinetic resolution of cyclopentenones.[76] High diastereomeric ratios and enantiomeric excesses were obtained for a number of 2,4-dialkylcyclopent-2-enones (**Scheme 4.5**). **Scheme 4.6** shows the reasoning behind the authors' choice of conditions for this resolution. As illustrated in **Scheme 4.3**, conjugate reduction of the enone generates a copper enolate. In the presence of a silane, σ-bond metathesis occurs to give a silyl enol ether product **106**. Under basic conditions, rapid racemisation of the starting material at the stereocentre α to the carbonyl will occur, but the product, as a silyl enol ether, will not undergo epimerisation. Screening revealed that the optimised conditions required stoichiometric NaO^{t}Bu as the base and PMHS as hydride source. ^{t}BuOH was required in order to speed up epimerisation to match the rate of conjugate addition. This methodology was applied in the total synthesis of Eupomatilone.[77]

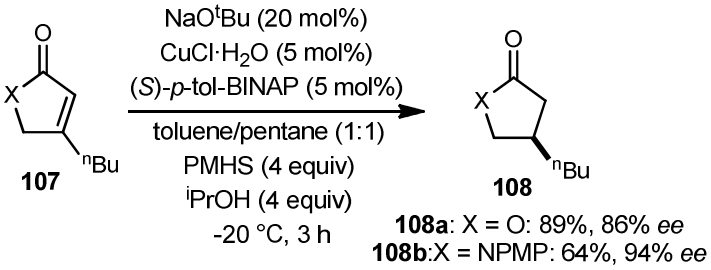


Scheme 4.5



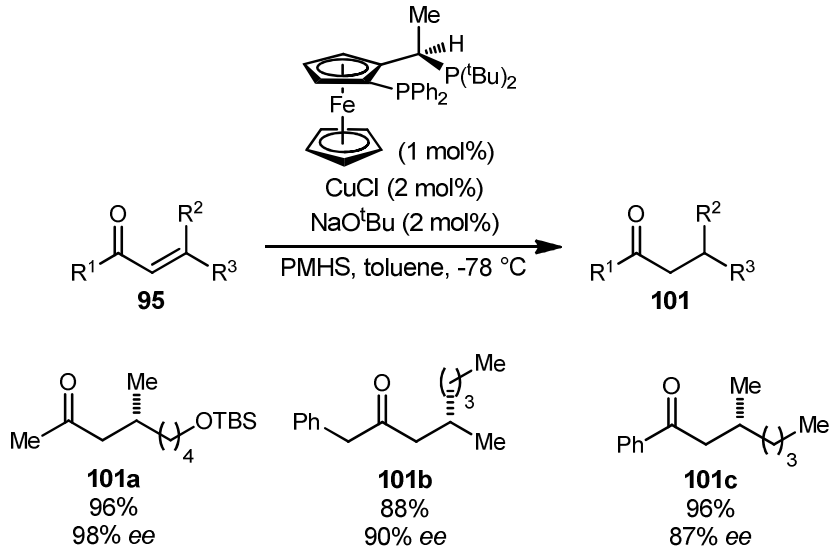
Scheme 4.6

The scope of the reaction has also been extended to cover α,β-unsaturated lactones and lactams (**Equation 4.1**).[78] The authors also disclose the use of bulky alcohols to accelerate catalyst turnover. This increase in turnover rate not only decreases reaction times, but also decreases the amount of side-product formation, thus increasing isolated product yields.



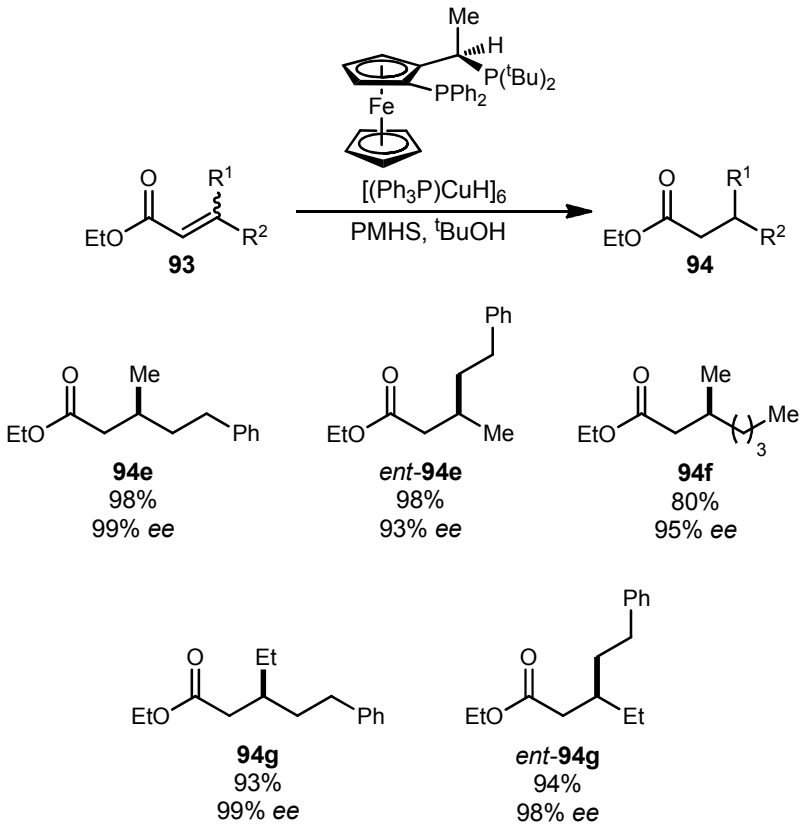
Equation 4.1

Up to this point, all of the catalytic reductions of enones that had been described were only effective for cyclic substrates. The first report of the CuH conjugate reduction of acyclic enones in high yields and enantiomeric excesses was published by Lipshutz in 2003.[79] Various bisphosphine ligands were employed, with those in the Josiphos class exhibiting the best results (**Scheme 4.7**).



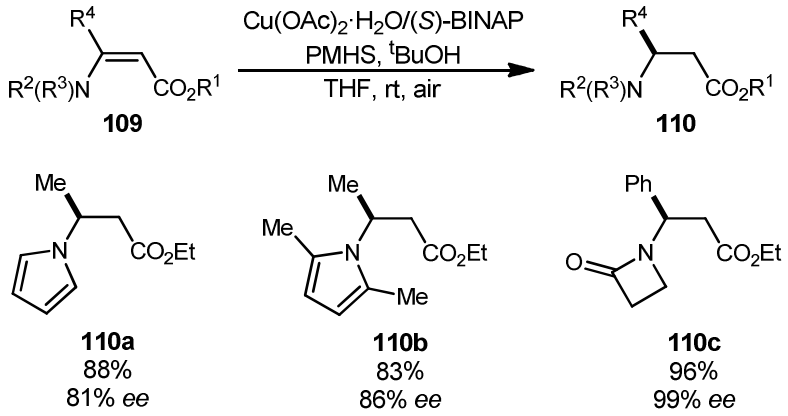
Scheme 4.7

Acyclic unsaturated esters have also been reduced in excellent yields and enantioselectivities (**Scheme 4.8**).[80] A catalyst loading as low as 0.1 mol% of Stryker's reagent could be successfully employed in conjunction with PMHS as stoichiometric reductant.



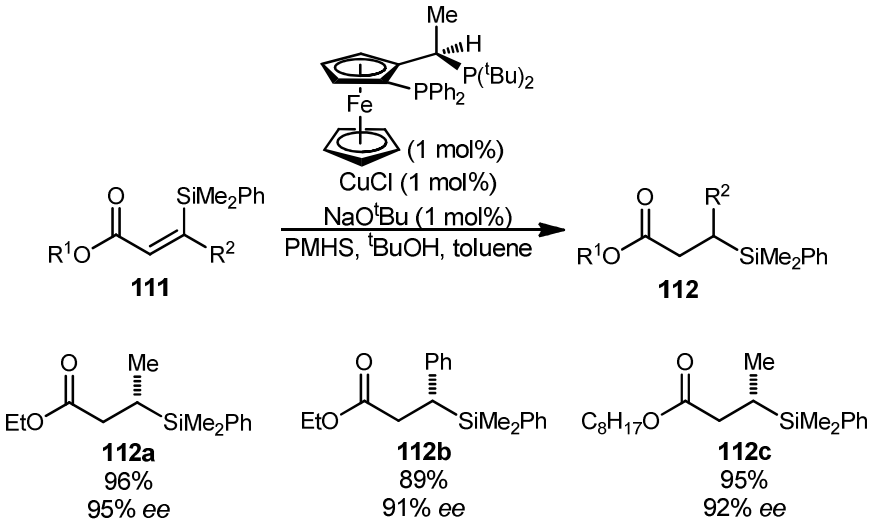
Scheme 4.8

Catalytic asymmetric conjugate reductions have also been applied to substrates containing a heteroatom on the *β*–carbon of the alkene as an approach to the synthesis of novel *β*-azaheterocyclic acid derivatives (**Scheme 4.9**).[81] A range of *β*-amino-substituted *α*,*β*-unsaturated esters were reduced in excellent yields and high enantiomeric excesses under conditions that did not require rigorous exclusion of air or moisture (a calcium sulphate guard tube was used). Substrates with bulky substituents in the *β*-position, such as **109c**, required long reaction times in order to go to completion. As moisture reacts competitively with the silanes, 6-10 equivalents of PMHS was used in these cases. This reaction has been utilised in the total synthesis of tricyclic myrmicarin alkaloids.[82]



Scheme 4.9

Another subset of α,β-unsaturated esters for which asymmetric CuH reductions have been reported are those with a β-silyl substituent.[83] Yields and enantiomeric excesses reported are generally above 90% although the reaction times required are higher than those for other esters (**Scheme 4.10**).

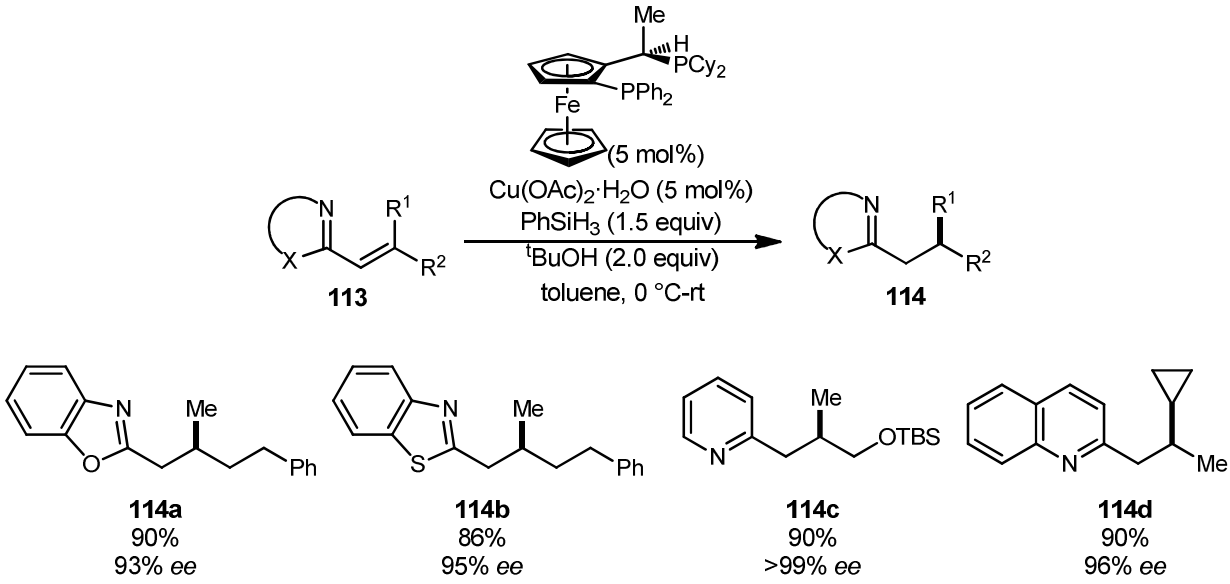


Scheme 4.10

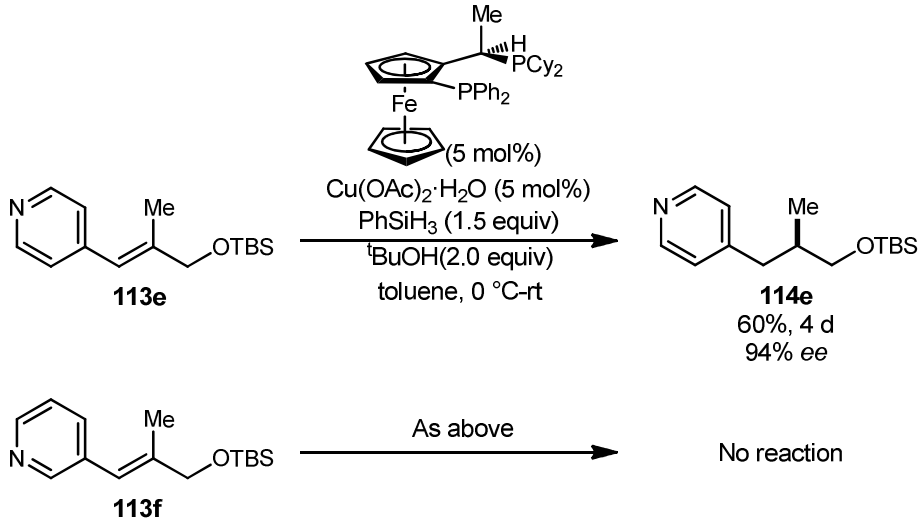
Enones and enoates are not the only unsaturated substrates that have been shown to undergo asymmetric copper hydride reductions. There have also been reports of the reduction of nitroalkenes[84] and α,β-unsaturated nitriles,[85] sulfones[86] and phosphonates.[87]

Within the Lam group, it has been shown that 2-alkenylheteroarenes are excellent substrates for asymmetric conjugate reduction chemistry.[88] Very high yields and *ee*s were obtained for substrates with varying heterocycles and with a range of substituents in the β-positions

(**Scheme 4.11**). Control experiments carried out on 3- and 4-alkenylheteroarenes have shown that a C=N group conjugated to the alkene is required for reactivity (**Scheme 4.12**).



Scheme 4.11

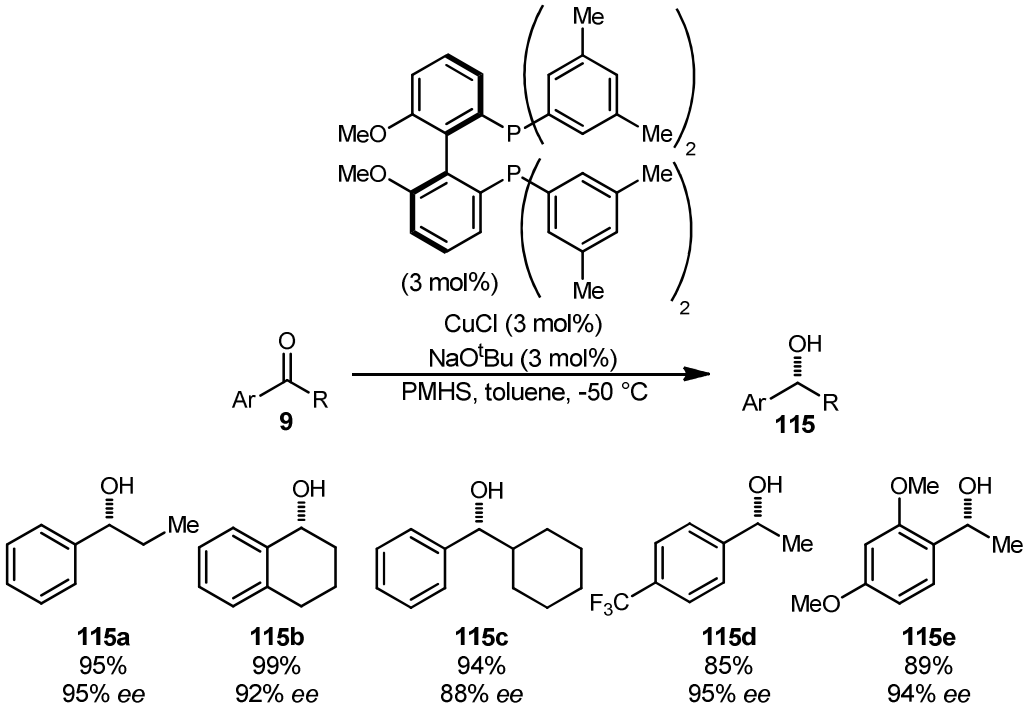


Scheme 4.12

Whilst in all the above examples conjugate reduction was observed, it is also possible to carry out the direct reduction of carbonyl compounds and imines using Cu-H chemistry.

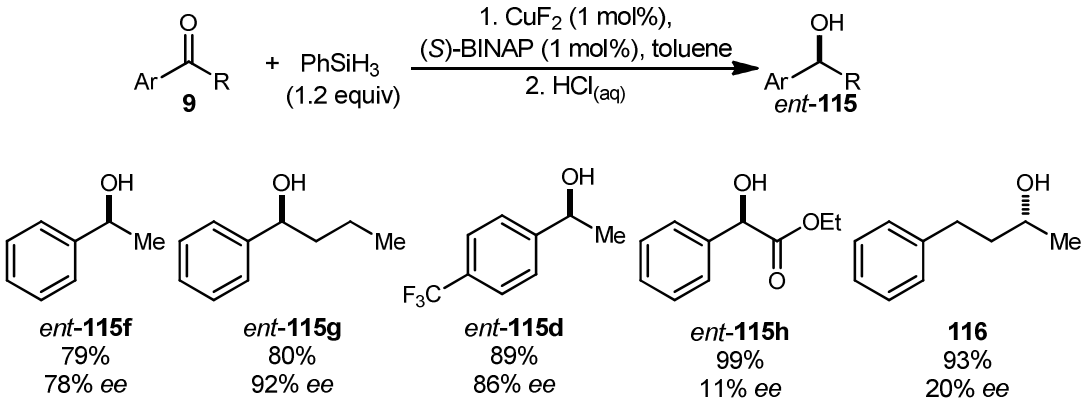
4.1.2 Asymmetric Copper-Catalysed Hydrosilylations of Carbonyl Compounds and Imines

The first published example of the application of the above described enantioselective CuH reduction chemistry conditions to carbonyl compounds was described by Lipshutz in 2001.[89] A range of aromatic ketones underwent hydrosilylation in excellent yields with high enantiomeric excesses (**Scheme 4.13**). With (*R*)-3,5-xylyl-MeO-BIPHEP as ligand and PMHS as hydride source at −50 ºC, ligand loadings as low as 0.005% allowed complete conversion to reduced product whilst retaining the high enantioselectivity.



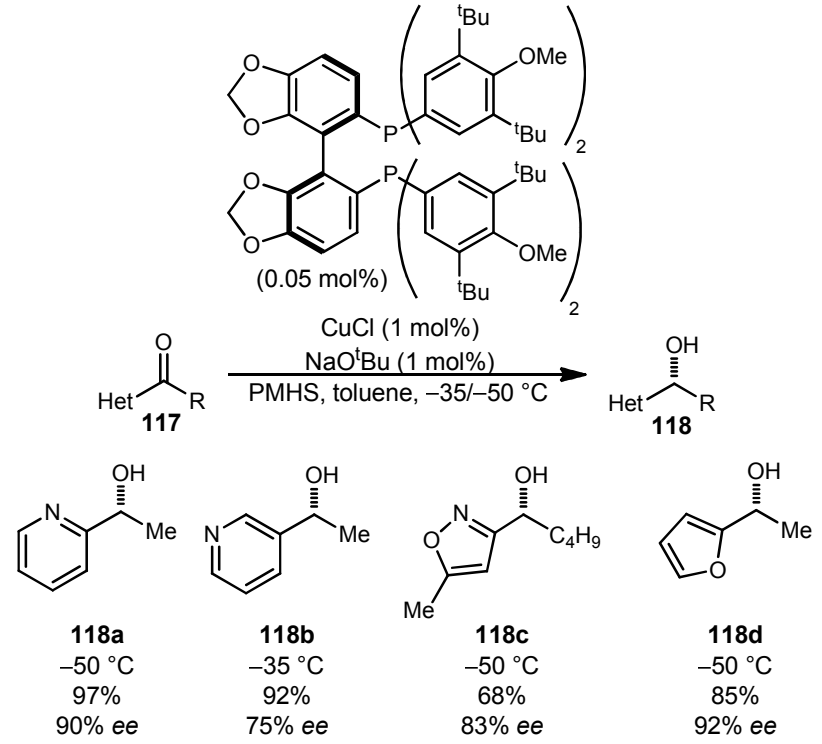
Scheme 4.13

At about the same time, the group of Riant published an asymmetric reduction of alkyl aryl ketones catalysed by a copper fluoride complex (**Scheme 4.14**).[90] (*S*)-BINAP was selected as a suitable chiral ligand and phenylsilane was preferred as hydride source, although cheaper reagents such as PMHS could be used if slower reaction rates were acceptable. Interestingly, this methodology used oxygen to accelerate the reaction, thus allowing decreased catalyst loadings to be employed. Yields are excellent for all examples shown and enantiomeric excesses are good to excellent with the exception of *α*-ketoester or dialkyl ketone substrates *ent*-**115** and **116**), although they are lower than those produced by Lipshutz (**Scheme 4.13**).



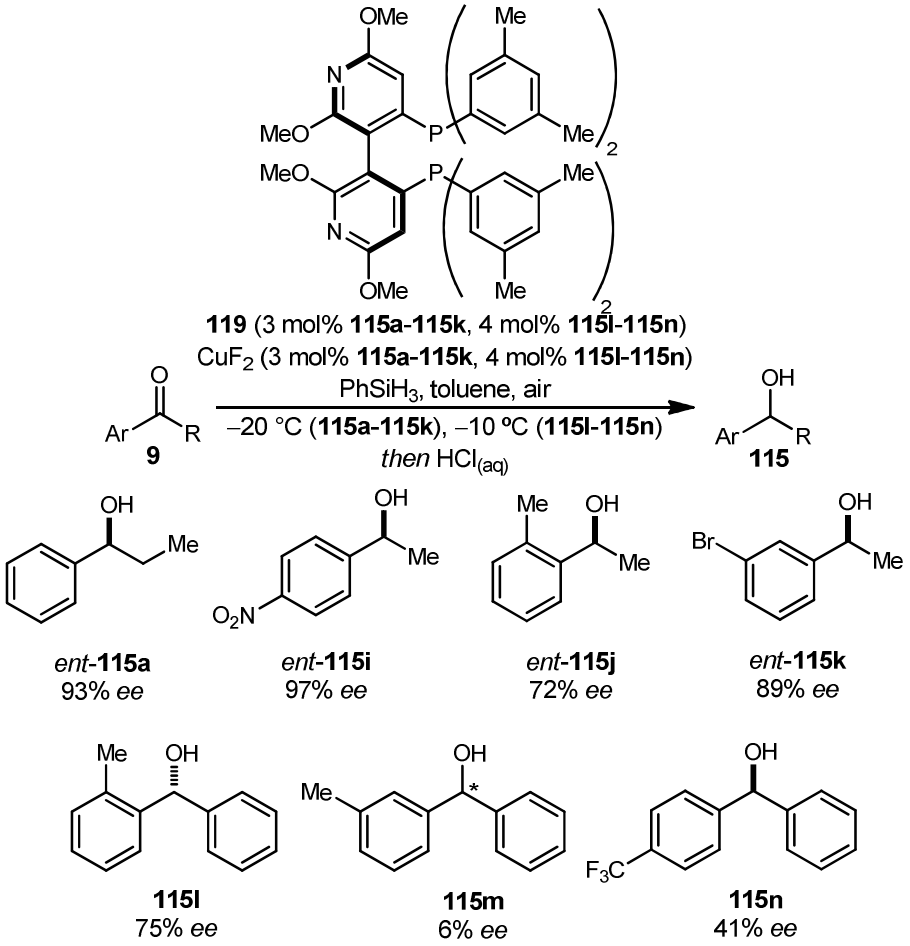
Scheme 4.14

Heteroaromatic ketones have also been reduced asymmetrically using copper hydride catalysis.[91] Pyridine, furan, thiazole and isoxazole substrates all underwent reaction under optimised conditions to give desired product in excellent yields and highly promising enantioselectivities (**Scheme 4.15**). Surprisingly, despite these successes, the pyrrole and thiophene equivalents did not give any conversion, even at room temperature. The reasons for this difference in reactivity are unclear.



Scheme 4.15

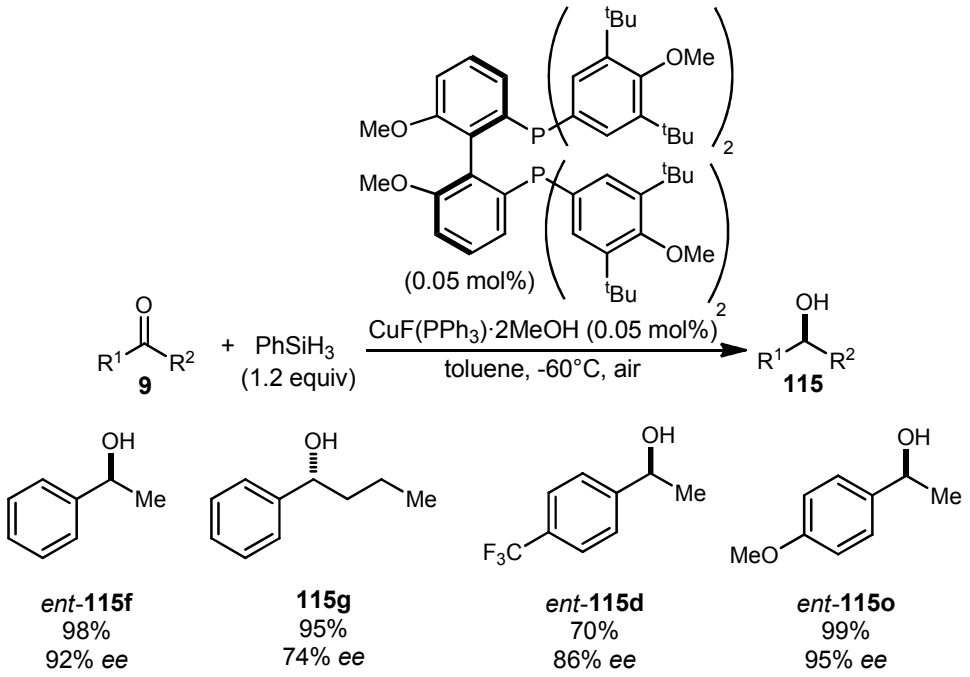
In 2005, Chan published a set of conditions for the asymmetric hydrosilylation of ketones, which combines the excellent enantioselectivities given by Lipshutz's conditions and the air and moisture stability of Riant's approach.[92] The authors also extended the substrate scope to include substituted benzophenones, although enantiomeric excesses for these examples were often lower (**Scheme 4.16**). No isolated yields are reported, but all conversions were >99%.



Scheme 4.16

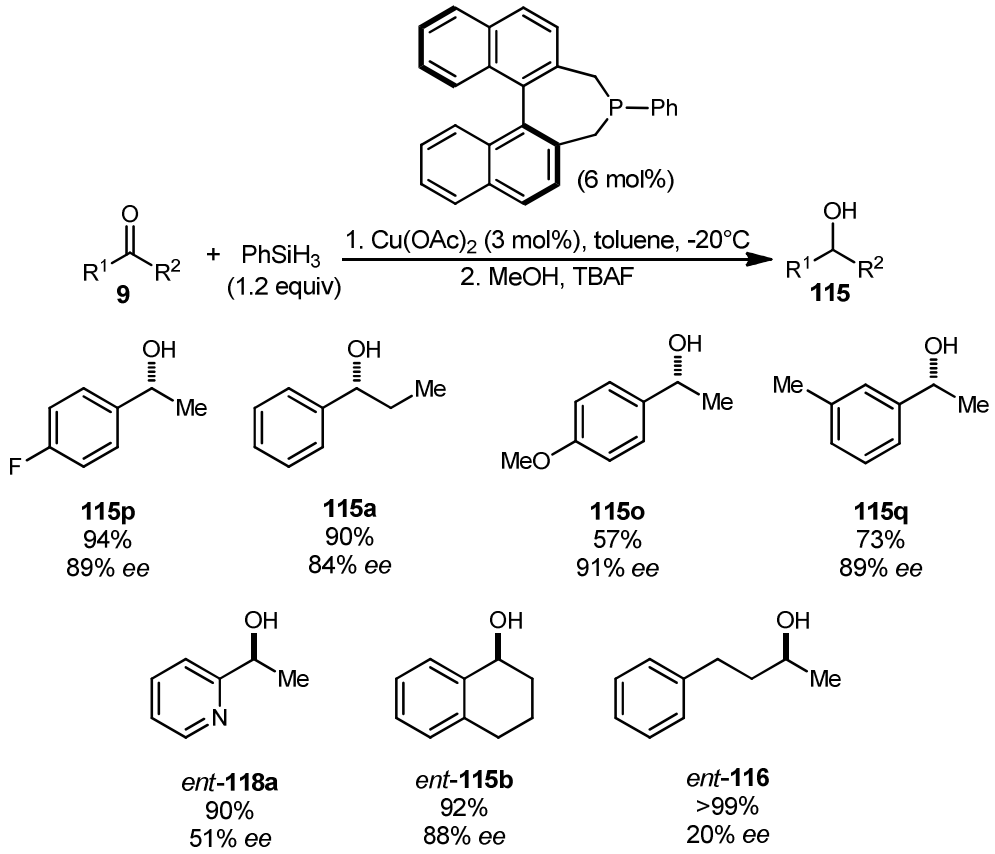
Riant has also published a detailed study on the effects of temperature and ligand structure in these enantioselective hydrosilylation reactions.[93] The authors discovered that strongly electron-donating bisphosphine ligands gave an accelerated reaction rate, but (*S*)-BINAP remained the ligand that gave the highest enantiomeric excess. The effect of temperature on *ee* was found to be more complicated. With (*S*)-BINAP or (*R*)-MeO-BIPHEP as ligand, there was a linear decrease in enantiomeric excess as the temperature was decreased until –40 °C at which point a minima was observed. A small increase in *ee* was then observed as the temperature was further decreased. This behaviour suggests that a change in mechanism

occurs at −40 °C. However, when a bulkier ligand ((*R*)-DTBM-MeO-BIPHEP) was employed, a linear increase in enantioselectivity was seen as the temperature was decreased. As a result of these studies, a new set of optimised conditions was obtained (**Scheme 4.17**).



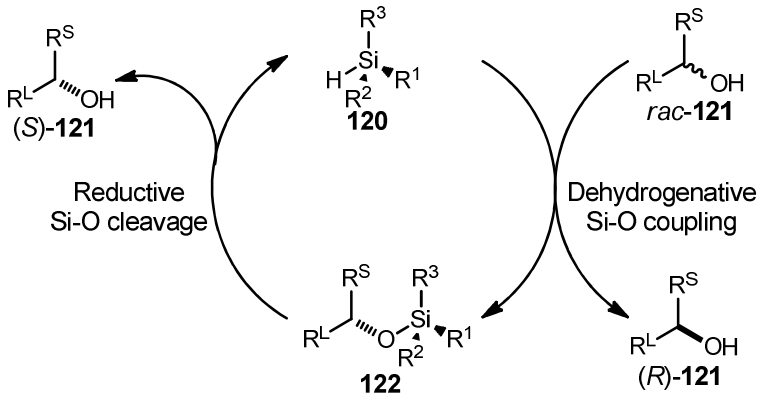
Scheme 4.17

Monodentate ligands have also been reported in asymmetric copper-catalysed hydrosilylations.[94] The optimised conditions gave generally high yields and enantiomeric excesses for the reduction of aryl alkyl ketones (**Scheme 4.18**). Extending the reaction to heteroaromatic and aliphatic ketones gave even higher yields, but *ee*s were variable for these substrates.



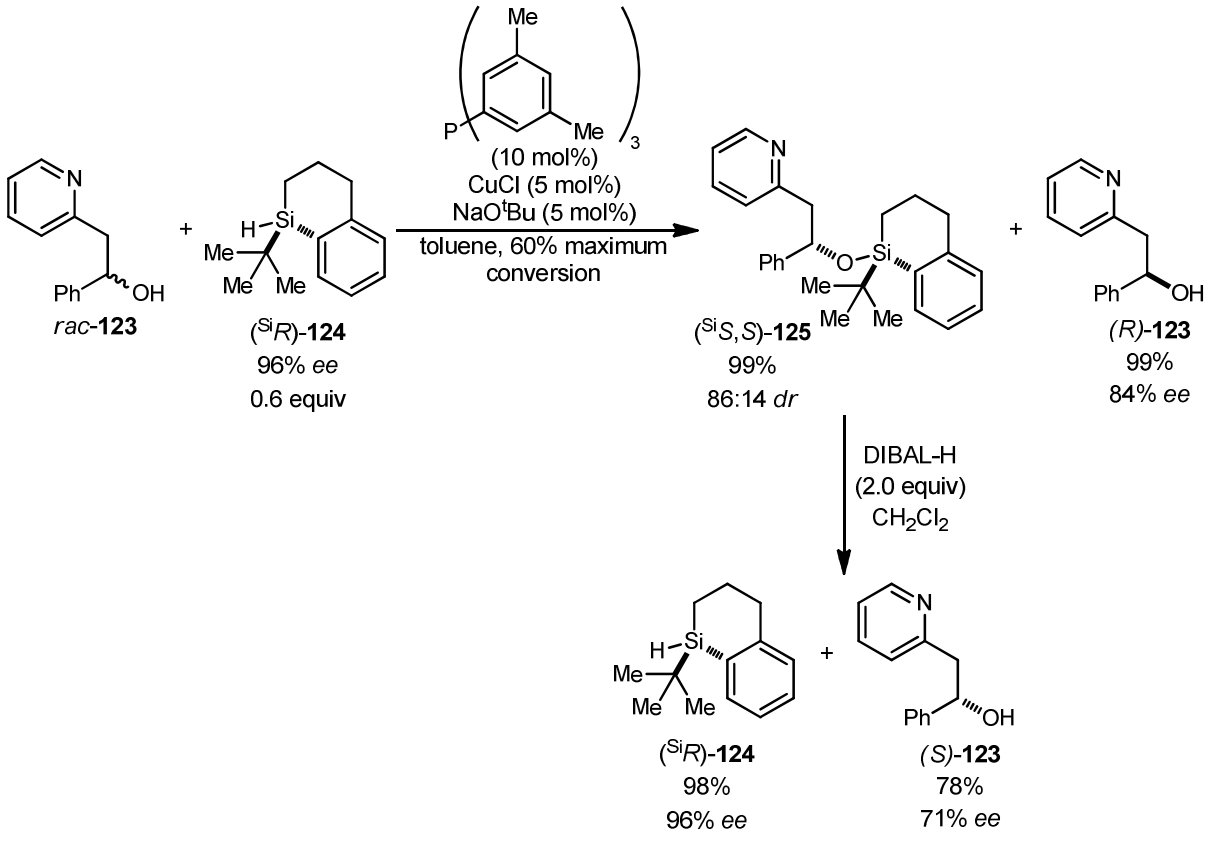
Scheme 4.18

A kinetic resolution of chiral secondary alcohols using copper hydride chemistry has been described by the group of Oestreich.[95] Their approach uses silanes which are stereogenic at the silicon centre. **Scheme 4.19** shows the logic behind the design of this resolution. If the stereogenic silane, **120**, reacts preferentially with one enantiomer of alcohol **121** to form one diastereomer of **122** then the opposite alcohol enantiomer will remain and be enantioenriched. Reductive cleavage of the Si-O bond would allow the silane reagent to be recycled and afford enantiomer (*S*)-**121** in high enantiomeric excess.



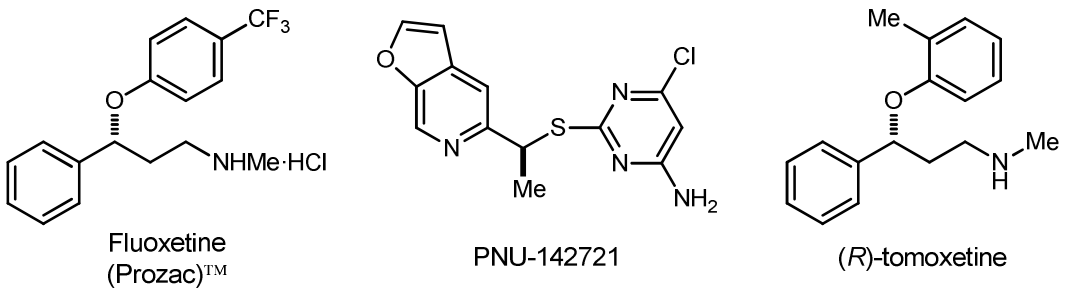
Scheme 4.19

Optimised conditions for the resolution are shown in **Scheme 4.20**. The yields of both obtained products are excellent across 7 racemic alcohol starting materials and *ee*s are good, ranging from 68-89%.



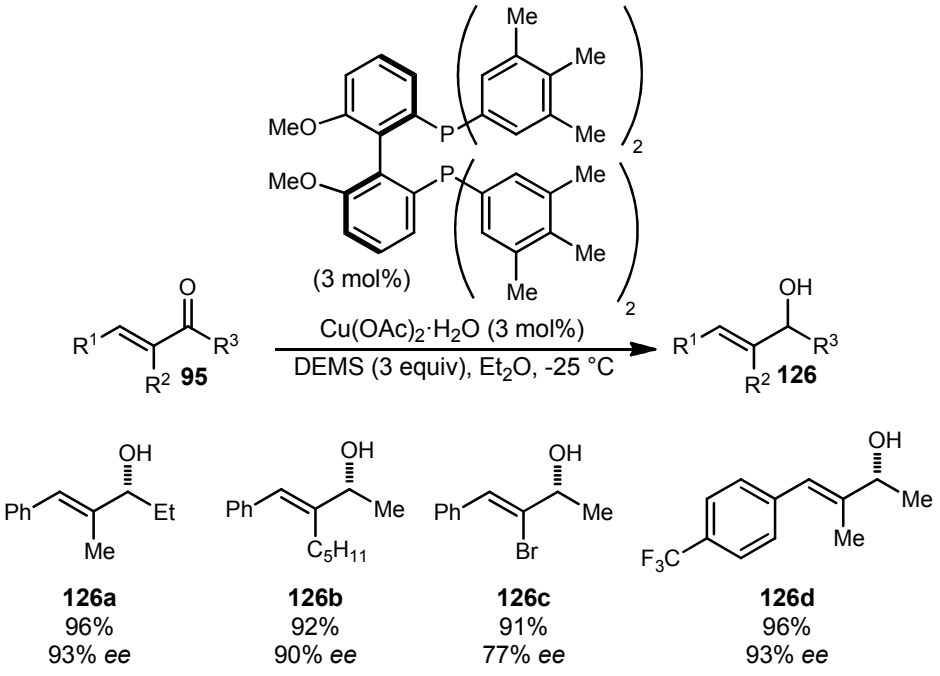
Scheme 4.20

Other applications of asymmetric hydrosilylation chemistry are given in a publication by the group of Lipshutz,[96] which displays the utility of this methodology through its use in the synthesis of several biologically active compounds (**Scheme 4.21**).



Scheme 4.21

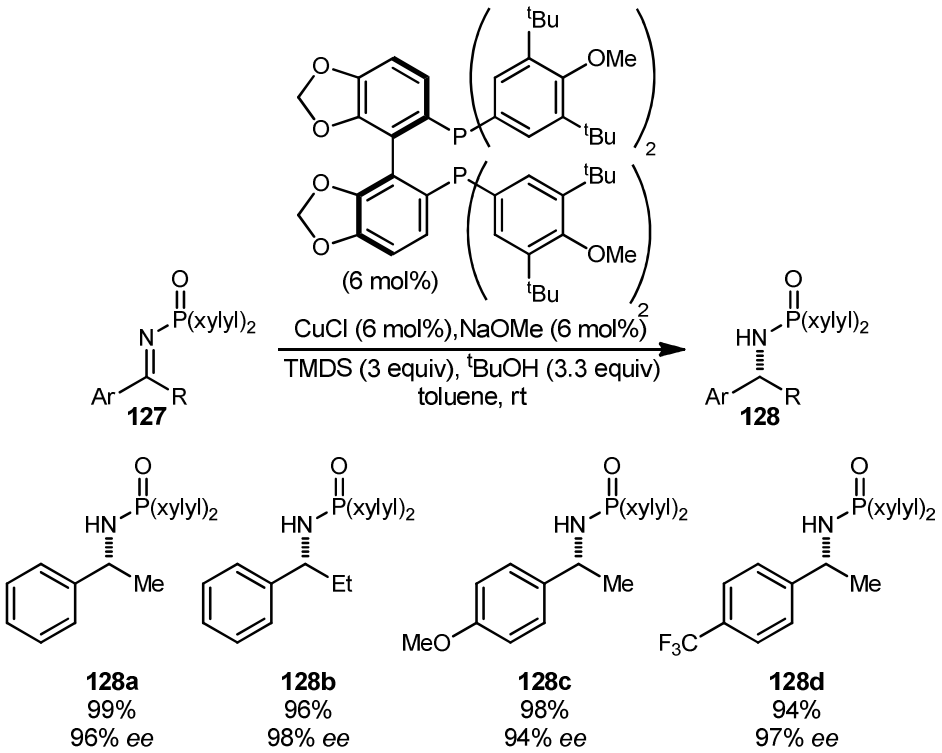
In 2010, Lipshutz published the first example of a selective, asymmetric 1,2 reduction of enones using CuH chemistry (**Scheme 4.22**).[97] A range of α-substituted enones were hydrosilylated in excellent yields with excellent enantiomeric excesses to give chiral allylic alcohols. The switch in selectivity for these substrates is believed to be due to the α-substituent sterically blocking the co-ordination of the copper species to the alkene moiety.



Scheme 4.22

Whilst all of the work described above employs chiral phosphorus ligands, other ligand classes can be used. In particular, NHCs have been shown to work extremely well in this chemistry.[98] However, there are currently no examples of the application of chiral NHCs in copper hydride reductions.

There has also been one report of the asymmetric hydrosilylation of imines under copper catalysis.[99] A phosphinyl residue was used as the substituent on nitrogen for several reasons. Firstly, these derivatives are easy to form and give a single isomer (*E*) at the C=N bond. It was also expected that the presence of the phosphorus would decrease the strength of the Cu-N bond in the intermediate formed after reduction, thus accelerating the rate of catalyst turnover. Optimisation of reaction conditions showed that TMDS was the best silane source, whilst (*R*)-DTBM-SEGPHOS gave the best enantiomeric excesses as ligand. A range of imines were reduced under these conditions to give the desired products with excellent yields and *ee*s (**Scheme 4.23**).



Scheme 4.23

Until recently, the mechanism of Cu-catalysed hydrosilylations was assumed to be similar to the proposed conjugate reduction mechanism (**Scheme 4.3**). However, a recent publication by Nikonov has cast significant doubts on this as a likely mechanism.[100] Using deuterium-

labelling experiments, the authors have shown that the hydride is transferred directly from the silicon species and not from the copper centre. On the other hand, the copper is required for the reaction to proceed. No alternative mechanism is proposed, but it is likely that the transition state involves both the silicon species and the copper-ligand complex. Further work is required for a full understanding of the mechanism of these hydrosilylation reactions.

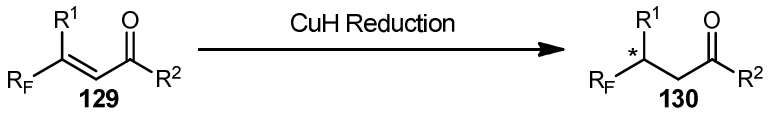
As we have seen, CuH reduction chemistry is a flexible method for the enantioselective synthesis of molecules from carbonyl compounds, whether α,β-unsaturated or not.

4.2 Results and Discussion

4.2.1 Enantioselective Copper-Catalysed Reductions of *β*-Fluoroalkyl-*α*,*β*-Unsaturated Ketones

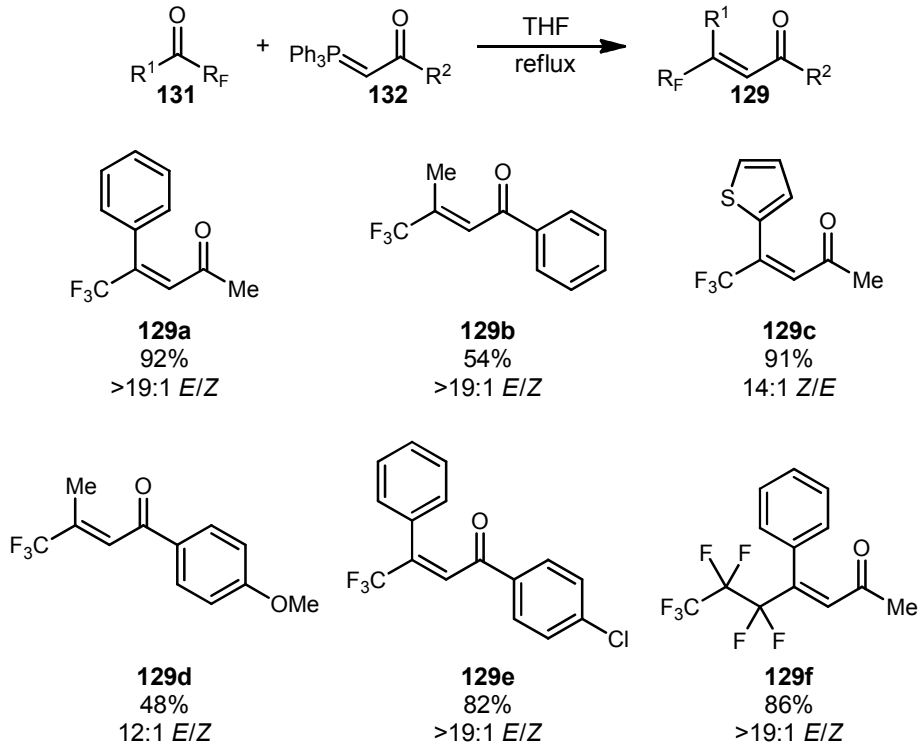
As we have seen, *β*-fluoroalkyl-*α*,*β*-unsaturated carbonyl compounds have been shown to be effective prochiral substrates in the asymmetric synthesis of chiral fluoroalkyl-containing compounds. However, the majority of conjugate additions carried out upon fluorinated enones have employed chiral auxiliaries. This makes such processes less atom-economic and requires additional steps for the addition and removal of the auxiliary. A more efficient approach could be developed through the use of asymmetric catalytic methodology. To this end, we have conducted an exploration of the reactivity of *β*-fluoroalkyl-*α*,*β*-unsaturated carbonyl compounds under established asymmetric metal-catalysed procedures.

The initial aim of this project was to develop a set of conditions for the asymmetric Cu-catalysed conjugate reduction of *β*-fluoroalkyl enones selectively generating a new stereocentre bearing a fluoroalkyl group (**Equation 4.2**).



Equation 4.2

Firstly, a selection of *β*-fluoroalkyl enones (**Scheme 4.24**) were synthesised from the commercially available fluoroalkyl ketones using Wittig chemistry. The reactions were conducted at reflux. Whilst the reactions go to completion within an acceptable time at lower temperatures, better selectivity of double bond geometry (up to >19:1) was obtained at reflux. Column chromatography was then used to separate the isomers.



Scheme 4.24 Yields shown are those of the isolated major isomer.

A method was then required for the identification of the geometry of the major isomer in each case. In order to achieve this, a ^{1}H-^{19}F HOESY (Heteronuclear Overhauser Effect Spectroscopy) NMR experiment was employed. This technique shows through-space correlations between protons and fluorine atoms. The signal indicated in **Figure 4.1** was taken to be diagnostic for the *E*-isomer in all cases except **129c** where it indicates the *Z*-isomer.

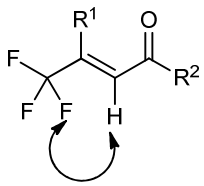
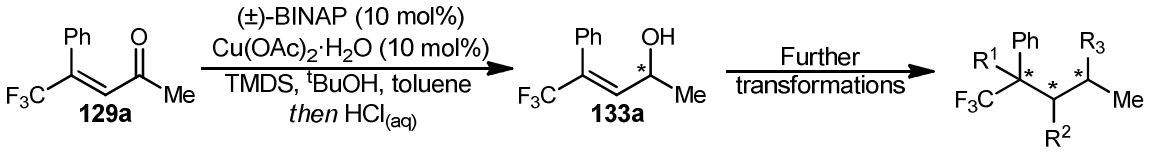


Figure 4.1

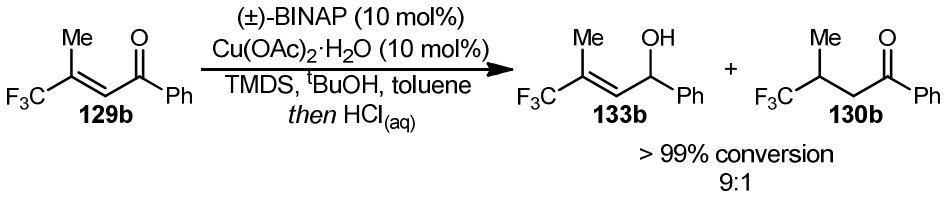
Enone **129a** was then subjected to some standard copper hydride reduction conditions. Initial conditions for the attempted reduction of **129a** were $Cu(OAc)_2 \cdot H_2O$ (10 mol%), (±)-BINAP (10 mol%), tetramethyldisiloxane (TMDS) as reductant (4 equiv), and ^{t}BuOH (4 equiv) in toluene at room temperature. To our surprise, the only obtained product was that of 1,2-reduction rather than the expected 1,4-reduction (**Equation 4.3**). Before the report published

by Lipshutz in 2010, there was no literature precedent for the direct Cu-catalysed reduction of carbonyl compounds in the presence of a conjugated double bond. Therefore, it was decided that this reaction warranted further investigation and screening for high enantiomeric excess. The products of the 1,2-reduction are chiral fluoroalkylated allylic alcohols. As there is a vast amount of established methodology for the manipulation of chiral allylic alcohols, it was expected that these species would make useful fluorine-containing chiral building blocks.



Equation 4.3

Before extensive screening was conducted, a substrate with a less bulky group than phenyl in the *β*-position (**129b**) was also tested in the reduction, as steric hindrance seemed a likely explanation for the switch in selectivity. Under the same conditions, **129b** was found to give 90% of the 1,2 reduction product, **133b**, and 10% of the 1,4 reduction product, **130b** (**Equation 4.4**). A control reaction also showed that in the absence of the copper catalyst, no reaction is observed.



Equation 4.4

Optimisation of the reaction conditions then began with the major aim being the development of an asymmetric reaction. The first reaction parameter that was explored was the chiral ligand. Selected results are shown in **Table 4.1**.

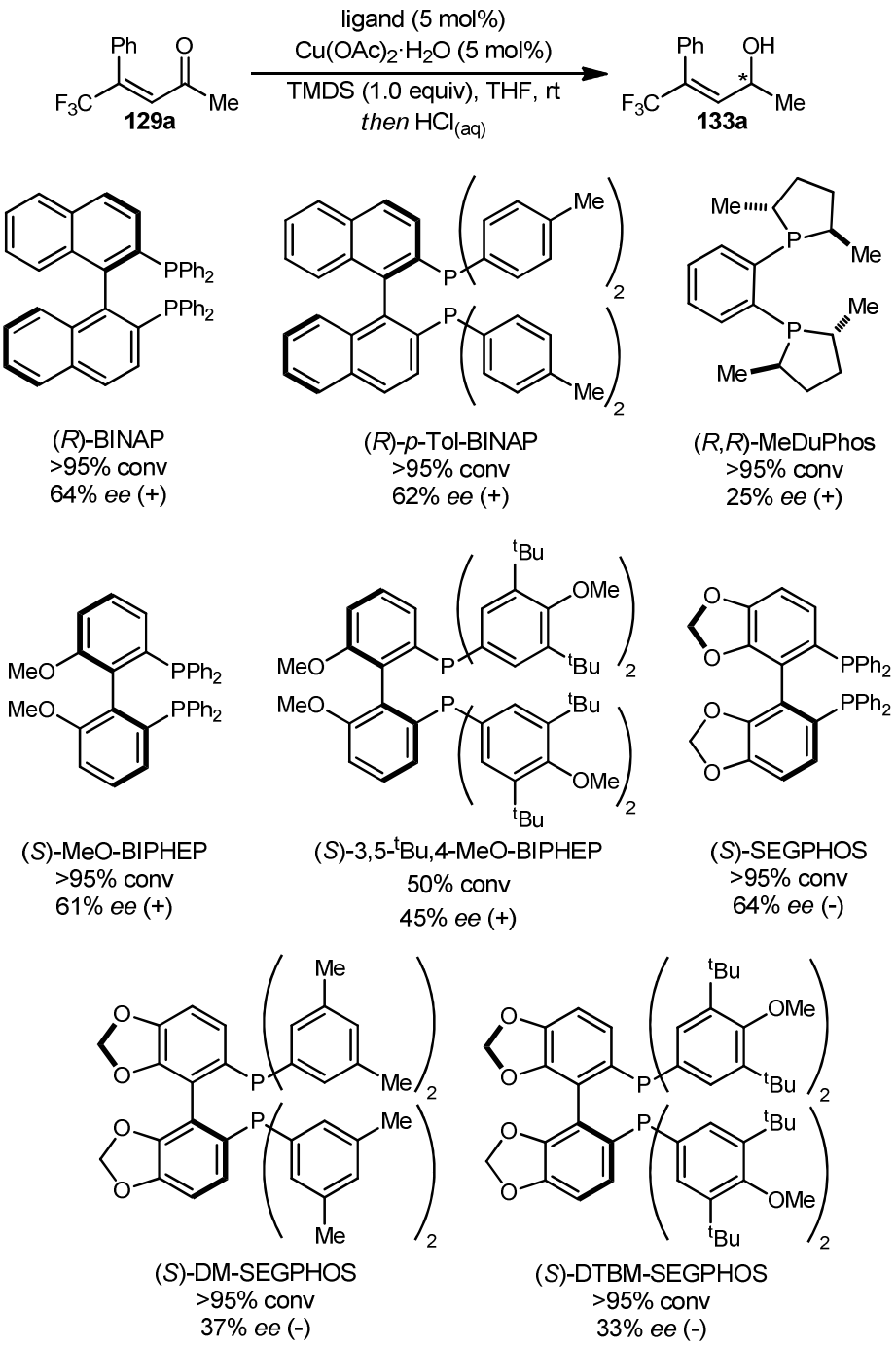
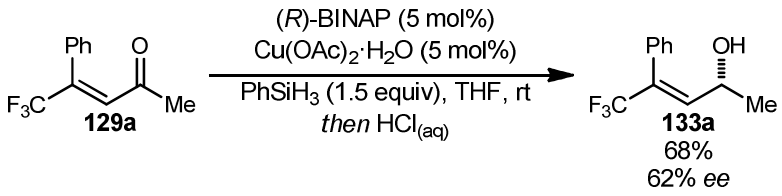


Table 4.1 Signs in parenthesis are those of the optical rotation.

An interesting observation made during ligand screening is that enantiomeric excesses decreased (sometimes very significantly) upon the employment of bulkier ligands within a certain class. For example, (*S*)-SEGPHOS gave an *ee* of 64%, whilst the much more hindered (*S*)-DM-SEGPHOS gave only 37%. Another, smaller, decrease in enantioselectivity (to 33%) was seen when the larger-still (*S*)-DTBM-SEGPHOS was used. (*S*)-SEGPHOS and (*R*)-BINAP were found to give the same *ee* value (although with the opposite enantiomers being

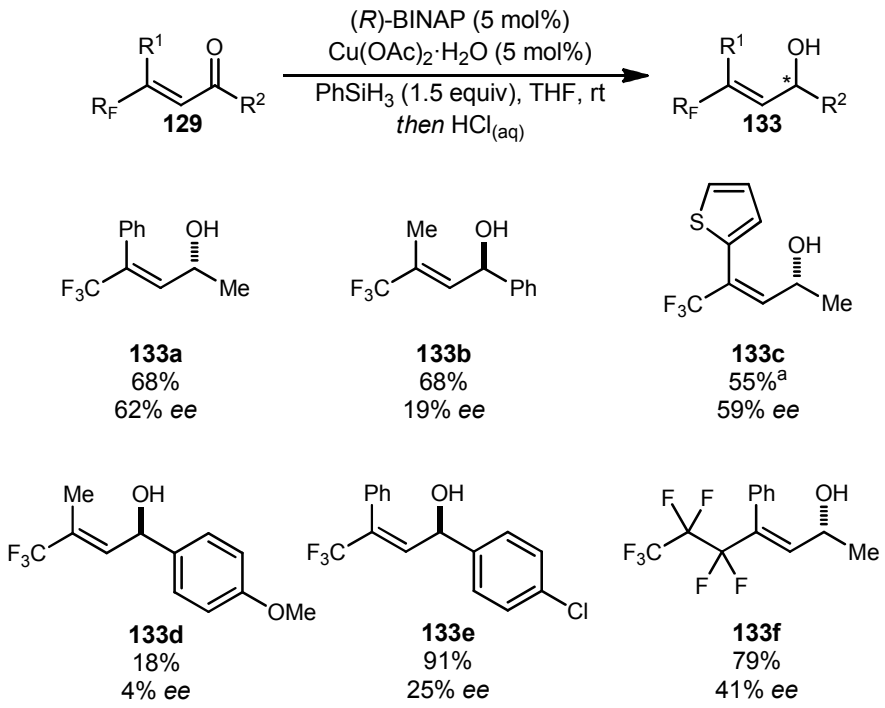
predominant) of 64%. None of the other bisphosphine ligands screened offered any improvement in this value. No reaction was observed when nitrogen-based ligands were tested.

Further screening of reaction conditions was carried out using (*R*)-BINAP as ligand. When the temperature was decreased to 0 °C, no improvement in enantiomeric excess was observed. Changing the copper source, solvent and the reductant employed often had an effect on conversions and reaction rates, but also failed to significantly increase the *ee*. However, the reaction was found to be cleaner when PMHS was used. The *ee* under these conditions was 68% and this was the highest that was observed during screening. Upon scale-up, extremely low isolated yields were observed with PMHS as hydride source. Switching to phenylsilane gave much improved yields, but a slightly decreased *ee*. The best conditions that were obtained as a result of this screening are given in **Scheme 4.25**.



Scheme 4.25

Other substrates were also tested under these conditions (**Scheme 4.26**). The enantiomeric excesses measured were found to be much lower when ketones other than methyl ketones were reduced. It is likely that this is a result of the decreased steric discrimination between the two sides of the ketone. Patterns were also observed with the ratio of 1,2- to 1,4-product obtained. For methyl ketone substrates (**129a**, **129c** and **129f**), no 1,4-product was seen. For **129e** with a bulky aryl substituent both adjacent to the carbonyl and in the *β*-position, only 1,2-product was obtained. However, for **129b** which has a much smaller methyl group at the *β*-position, as well as a phenyl ring adjacent to the carbonyl, there was a 3:1 ratio of 1,2- to 1,4-reduction. **129d**, which has these characteristics in conjunction with an electron-donating substituent on the aromatic ring making the ketone less electrophilic, gave a 1:1.6 ratio of 1,2- to 1,4-addition of hydride.



Scheme 4.26 Yields given are those of isolated product. Reactions were conducted on 0.5 mmol of unsaturated ketone. [a] Isolated as a mixture with **134**.

Whilst complete conversion to reduction product was seen for all other substrates tested, a side-product (from which the reduction product was found to be inseparable) was observed for **129c** that constitutes 25% of the reaction mixture. This product, difluoroalkene **134**, is most likely formed by a Cu-F interaction followed by reduction of the ketone.

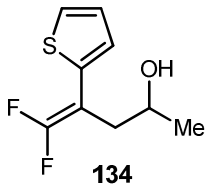
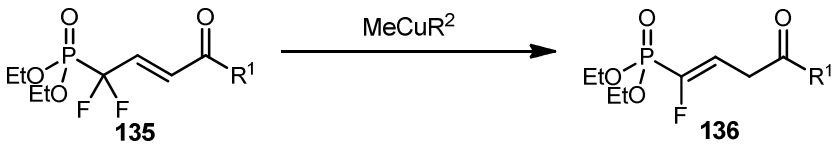


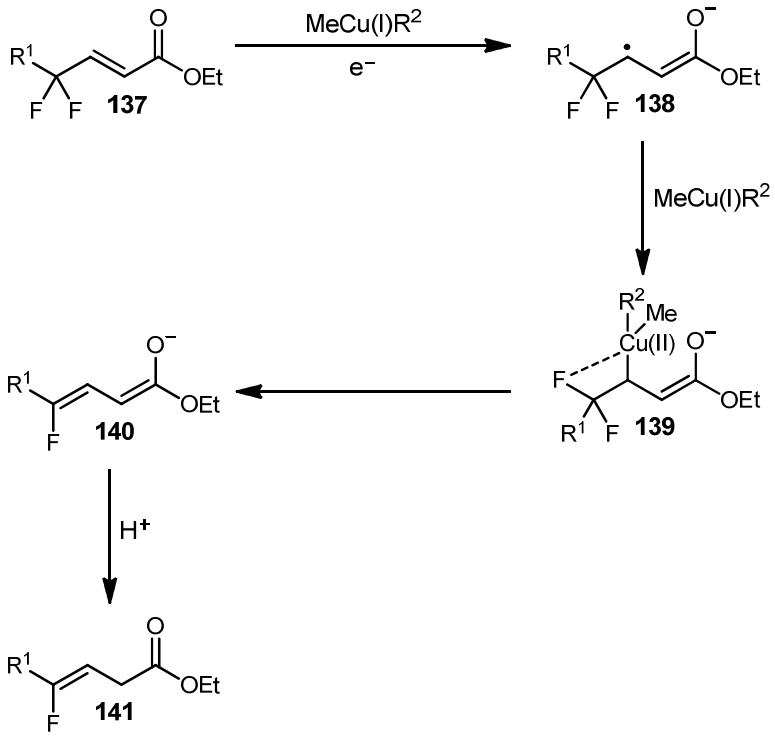
Figure 4.2

There are a few reports in the literature of reductive defluorinations catalysed by metal species, specifically organocopper reagents[101,63] or samarium iodide.[102] For example, the group of Otaka have reported the synthesis of phosphopeptide mimics employing the organocopper-catalysed reductive defluorination of γ-difluoro-α,β-unsaturated carbonyl compounds (**Scheme 4.27**).[101a), 102]



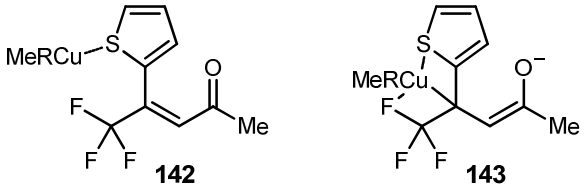
Scheme 4.27

A mechanism for this process has been proposed (**Scheme 4.28**).[103] A single electron transfer from the copper species generates radical **138**, which forms **139** through the addition of another molecule of the copper reagent. Interaction of the copper with a fluorine atom then leads to *β*-elimination to give **140**.



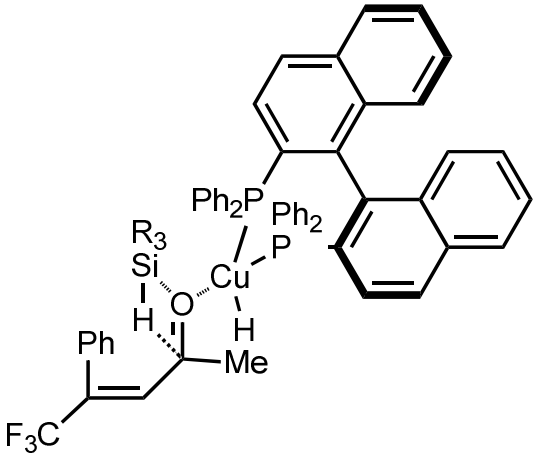
Scheme 4.28

It is not known why this product should be formed from **129c** and not for the other ketones, but a possible explanation is that an initial co-ordination to the sulphur atom of the thiophene moiety encourages the initial single electron transfer or the addition of copper into the molecule (**Scheme 4.29**).



Scheme 4.29

A possible transition state for the 1,2-reduction is given in **Scheme 4.30**. Evidence from the work of Nikonov[100] suggests that both the copper hydride complex and silane are involved in the transition state. Co-ordination of the copper hydride species to the oxygen (at the least hindered lone pair) could activate the carbonyl group towards attack from the silane. The *si* face is sterically blocked by the chiral ligand, resulting in addition of the hydride to the *re* face.



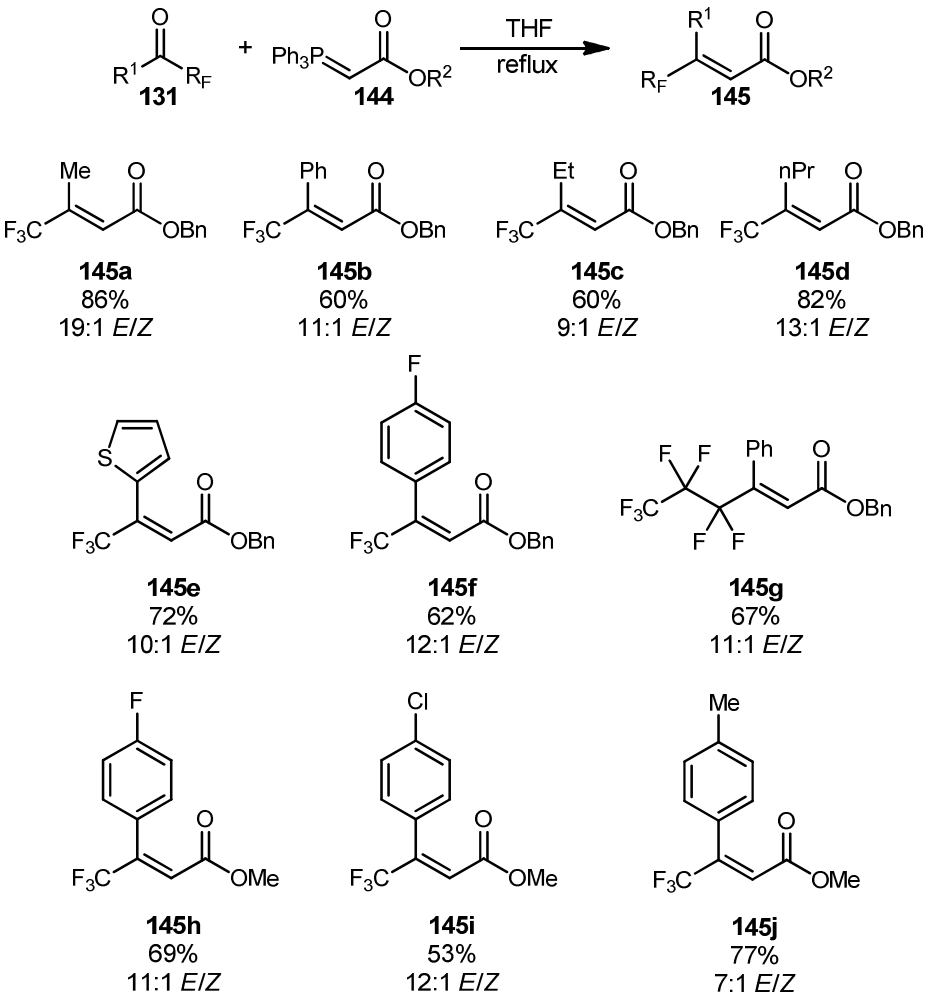
Scheme 4.30

At this point, as no further improvement to the enantiomeric excesses was being observed for the 1,2-reduction, we returned to our original aim of generating the fluoroalkyl stereocentre by 1,4-reduction. In order to achieve this, we investigated the reaction of *β*-fluoroalkyl *α*,*β*-unsaturated esters.

4.2.2 Enantioselective Copper-Catalysed Reductions of *β*-Fluoroalkyl-*α*,*β*-Unsaturated Esters

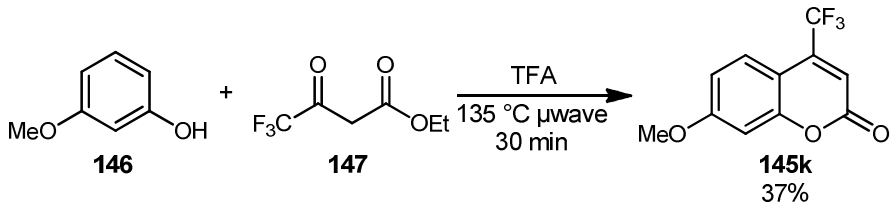
The lower electrophilicity of esters relative to ketones was expected to encourage the 1,4-reduction over the 1,2-reduction in the reaction of *β*-fluoroalkyl-*α*,*β*-unsaturated esters under copper hydride conditions.

The first requirement was the synthesis of the substrates. In most cases, a straightforward Wittig reaction could be conducted as it had been for the synthesis of ketone substrates. A total of ten compounds were made in this way (**Scheme 4.31**).



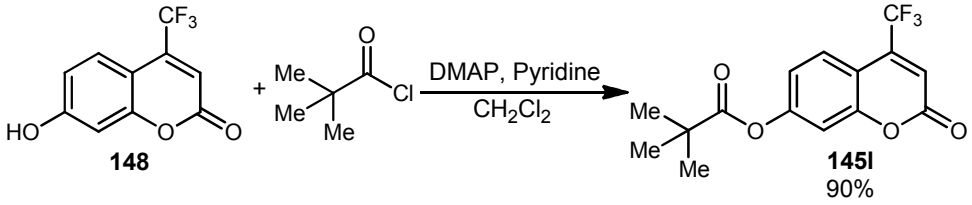
Scheme 4.31 Yields are those of isolated major isomer.

Two cyclic substrates were also synthesised. A Von-Pechmann cyclisation from trifluoroacetoacetate and phenol **146** provided **145k** in 37% yield (**Equation 4.5**).



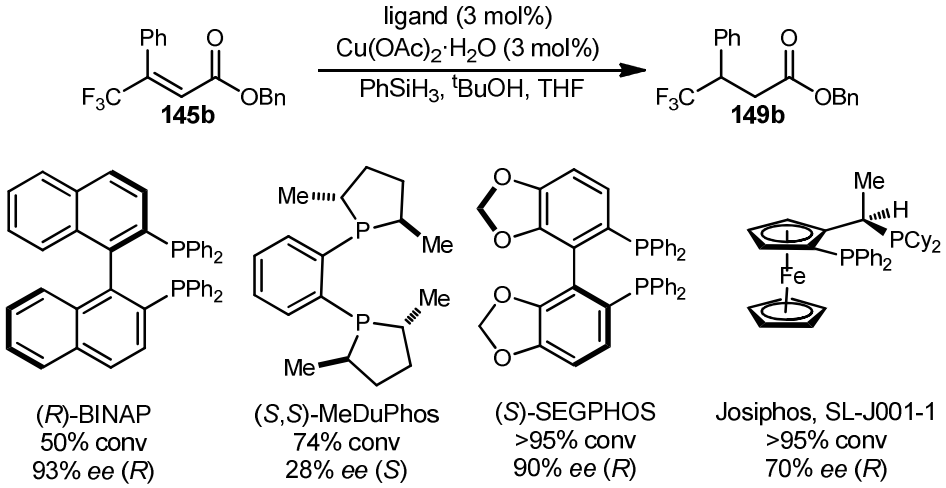
Equation 4.5

145l was synthesised by an ester formation reaction on the commercially available phenol (**Equation 4.6**).



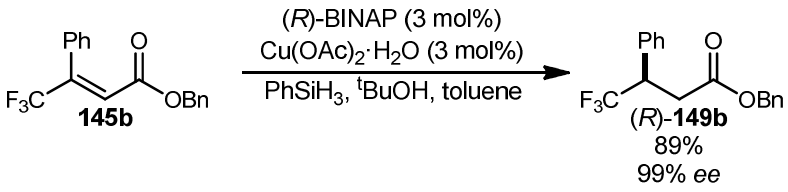
Equation 4.6

Initial screening was mostly conducted on **145b**. Ligands were investigated first (**Scheme 4.32**). Josiphos gave complete conversion to product, but the enantiomeric excess measured was a disappointing 70%. (*R*)-BINAP gave an *ee* of 93%, but 50% of the starting material remained. (*S*)-SEGPHOS showed promise, giving complete conversion and an excellent *ee*, whereas *(S,S)*-MeDuPhos gave much poorer results.



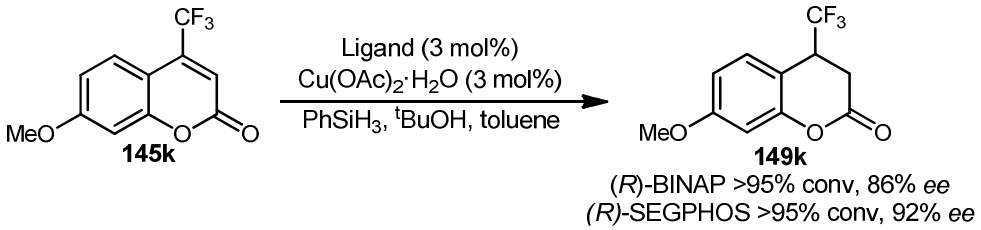
Scheme 4.32

Decreasing the reaction temperature to 0 °C with Josiphos as ligand gave an increase in enantiomeric excess to 86%. Changing the reaction solvent to toluene had no effect on the conversion or the *ee* value obtained when Josiphos was used as the ligand. However, when (*R*)-BINAP was employed with toluene as solvent, complete conversion to desired product was observed and the enantiomeric excess was an excellent 99%. Conducting the reaction on a larger scale (0.5 mmol) gave 89% isolated yield (**Equation 4.7**).



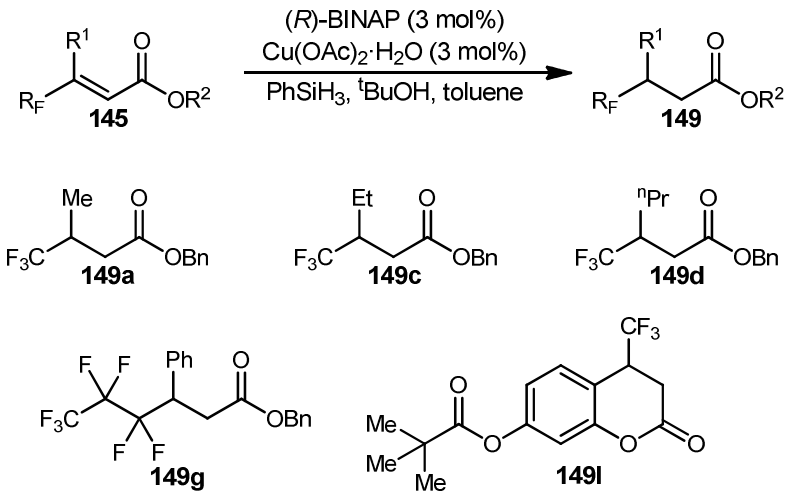
Equation 4.7

One other substrate for which the reduction was successful with the above conditions was **145k** giving complete conversion and an ee of 86% (**Equation 4.8**). For this substrate, (*R*)-SEGPHOS gave a better enantiomeric excess of 92% without impacting upon the obtained conversion.



Equation 4.8

Unfortunately, when these conditions were extended to other substrates, numerous problems were encountered. Whilst complete or near complete conversion to the desired products was obtained for almost all starting materials with the optimised conditions from **Equation 4.7**, enantiomeric excesses could not be measured for some due to a lack of effective racemic assay conditions. Multiple chiral HPLC and GC columns were tested, but no separation of the enantiomers was observed for those products shown in **Scheme 4.33**. The use of Pirkle's reagent to obtain a chiral NMR assay was also found to be unsuccessful. Derivatisation of the products to give compounds for which the enantiomers can be resolved is a potential solution. Care must be taken with such an approach, however, as the conditions used to obtain derivatised product must not cause any change to the enantiomeric excess.



Scheme 4.33

The enantiomeric excess obtained for the reduction of **149e** with (*R*)-BINAP as ligand was a good 94%. Unfortunately, for this substrate, an additional product was also formed (**150**, **Figure 4.3**), which was inseparable from the desired product. This side product is formed through a Cu-F interaction leading to *β*-elimination (see **4.2.1**). Traces (<<5%) of this product are observed with other substrates. The reasons for the large increase in the amount of difluoroalkene product in this case are unknown, although the thiophene containing ketone (**129c**) was also found to give increased amounts of the elimination product in the 1,2 reduction (*vide supra*). The exact quantity of this side-product obtained varies depending upon the ligand employed, but 25-35% was found to be typical.

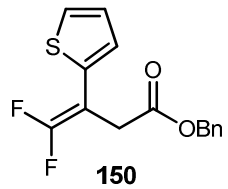
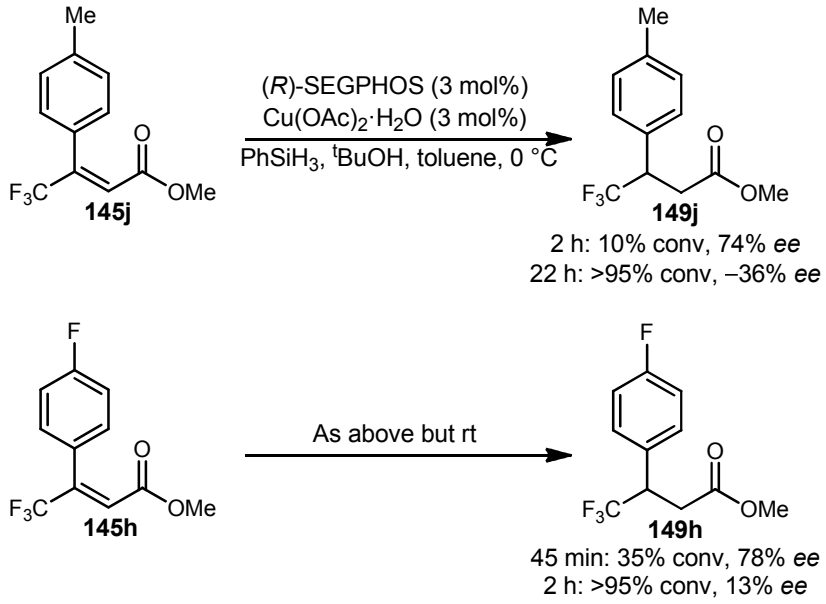


Figure 4.3

The final set of substrates for which problems were observed are **145h** and **145j**. **145j** was subjected to the optimised conditions with varying ligands and monitored by GC analysis. After 2 hours reaction time with (*R*)-SEGPHOS as ligand at 0 °C, only 10% conversion into desired product was observed and the enantiomeric excess was measured as a promising 74%. However, after 22 hours, complete conversion to the reduced product was seen, but with an *ee* of 36% of the opposite enantiomer (**Scheme 4.34**). The more reactive, electron-deficient, substrate **145h** was exposed to the same conditions. After 45 minutes at room

temperature, the conversion was already at 35% with an *ee* value of 78%. No starting material remained after two hours, but the *ee* had significantly decreased to 13%.



Scheme 4.34

Early consideration on the possible cause of the change in enantioselectivity as the reaction progressed for these substrates produced several possibilities which were explored in turn. Firstly, it is possible that the gradual build-up in the reaction mixture of compounds **151, 152** and **153** (**Figure 4.4**) was affecting the course of the reaction (**153** can be observed by GC-MS as the reaction progresses). This species is formed by the reaction of either the hydride source itself, or the silyl enol ether intermediate, **154** (**Figure 4.4**), with the proton source, ^{t}butanol. Other silanes containing only one hydride group (Et_3SiH and $(EtO)_3SiH$) were tested in the reaction, but gave only a trace of the desired product. PMHS was also tried and gave 35% conversion with an *ee* of only 20%. This possible explanation was finally ruled out when the reaction was conducted in the absence of ^{t}butanol. Whilst the reaction of **145h** was slower without the proton source, complete conversion to the desired product was still observed and the enantiomeric excess was similar to that seen in its presence (21%).

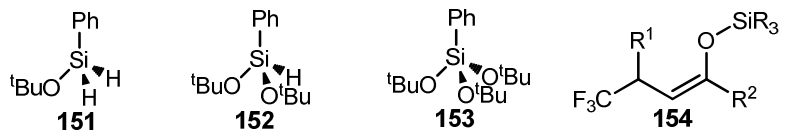
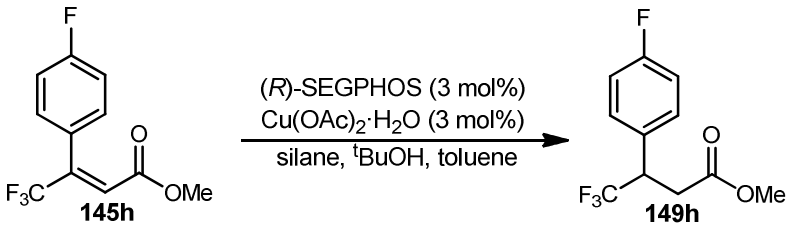


Figure 4.4

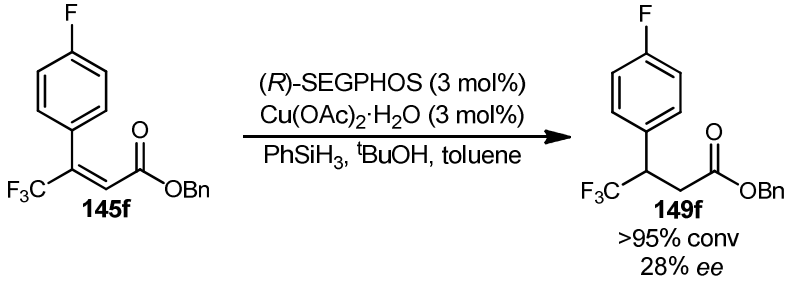


Silane	Conversion (%)	ee (%)
$PhSiH_3$	>95	13
PMHS	35	20
Et_3SiH	<5	-
$(EtO)_3SiH$	<5	-
[a]$PhSiH_3$	>95	21

Table 4.2 [a]No ^{t}BuOH was added

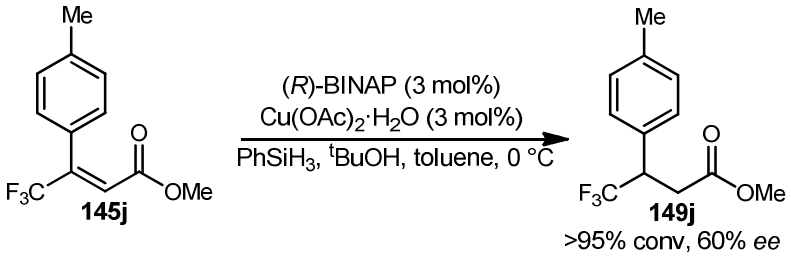
Another possible explanation for the changing enantiomeric excess as the reaction progresses is a selective degradation of one enantiomer in the chiral environment of the reaction mixture. This is unlikely to be the cause due to good isolated yields of the desired reduction product (70% for **149h** and 76% for **149j** when the reaction was carried out racemically employing (±)-BINAP).

As there are only two small differences between these substrates and **145b** for which the reaction worked well and completed in high enantiomeric excess, it stands to reason that one of these changes is responsible for the poorer enantioselectivity. One is the presence of a *para*-substituent on the aromatic ring in the *β*-position and the other is a methyl ester in place of the benzyl. **145f** was synthesised to investigate the effect of the ester group. Under the same reaction conditions with (*R*)-SEGPHOS as ligand again, an *ee* of 28% was obtained, showing that the effect of the ester group is minimal (**Equation 4.9**).



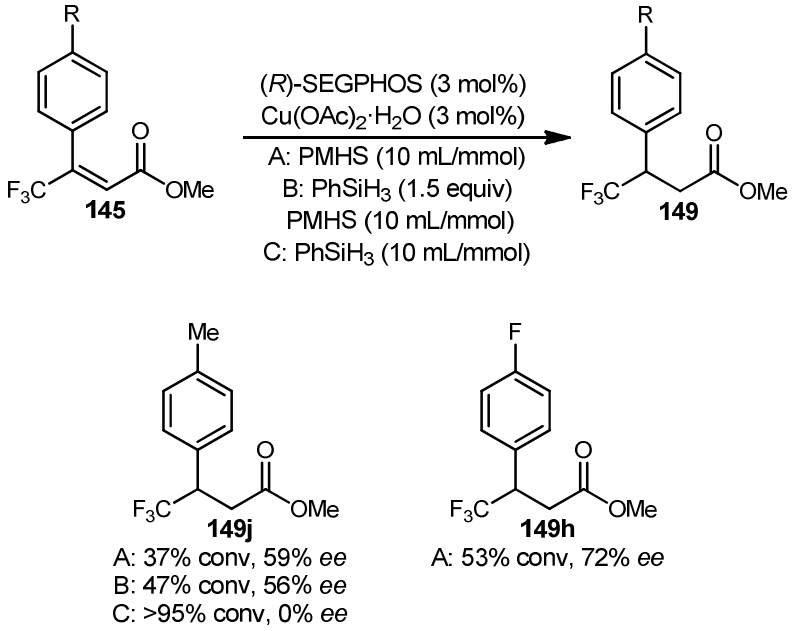
Equation 4.9

Further screening was carried out on these compounds in the hope that more results would shed some light on the cause of these *ee* issues. Whilst some improvement was observed upon screening other ligands (BINAP gave complete conversion and 60% *ee* for **149j**), the enantiomeric excesses still remained disappointing (**Equation 4.10**). Whilst decreasing the reaction temperature from room temperature to 0 °C had a positive effect on the enantioselectivity (13% to 42% for **149h** with >95% conversion), decreasing the temperature further to −10 °C gave no improvement.



Equation 4.10

Using PMHS as a reaction solvent instead of just as a hydride source gave increased *ee* values (59% for **149j** and 72% for **149h**). Unfortunately, the conversions obtained were low as no improvement was seen on those values obtained with PMHS as a reagent (37% for **149j** and 53% for **149h**, **Scheme 4.35**). Interestingly, with PMHS as solvent, the *ee* value remained roughly the same throughout the reaction with the value for **149h** being 68% at 36% conversion. With the aim of increasing these conversions, phenylsilane was added as a hydride source whilst PMHS remained as solvent. This gave a small increase in conversion (up to 47% for **149j**), whilst the *ee* remained almost the same. Using phenylsilane itself as solvent led to a very rapid reaction, but completely racemic product was obtained.



Scheme 4.35

Whilst the results for this reaction were initially highly promising and it does work extremely well for some substrates (**145b** and **145k**), problems with extending the methodology to other compounds limits its utility as a synthetic method.

4.3 Conclusions and Future Work

The reactivity of β-fluoroalkyl-α,β-unsaturated carbonyl compounds under copper-hydride reduction conditions was studied. Whilst most unsaturated ketones underwent 1,2-reduction, the unsaturated esters were found to reduce in the 1,4 sense. Screening for enantioselectivity for the ketone substrates gave moderate enantiomeric excesses of up to 62% for methyl ketones, but the results were found to be much poorer with bulkier groups. The 1,4-reduction was found to work extremely well for some substrates giving *ee*s of up to 99%, but the reaction was found to be of limited generality and therefore of limited use as a synthetic strategy. Problems were encountered with obtaining racemic assays for several substrates meaning that enantiomeric excesses could not be measured.

Possible solutions to the problems observed with this chemistry mostly involve the investigation of alternative catalyst systems (both metal and ligand) for conjugate reduction. The potential utility of the products (containing as they do a fluoroalkyl-bearing stereocentre) would make this a worthwhile endeavour.

4.4 Experimental

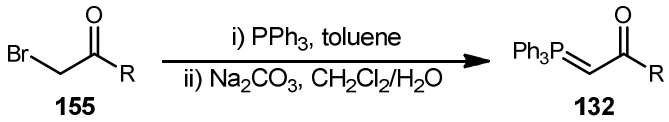
General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. THF, toluene and dichloromethane were dried and purified by passage through activated alumina columns using a solvent purification system. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or vanillin as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[40] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film or as a dilute solution in $CHCl_3$, or on a Shimadzu IRAffinity-1 instrument as a thin film or as a solid. ^{1}H NMR spectra were recorded on a Bruker AVA500 (500 MHz) spectrometer, a Bruker AVA400 (400 MHz) spectrometer, a Bruker ARX250 (250 MHz) or a Bruker DPX360 (360 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm; CD_3OD at 4.84 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker AVA500 (125.8 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm; CD_3OD at 49.05 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker ARX250 (235 MHz) spectrometer or a Bruker AVA400 (376 MHz). Chemical shifts are reported in parts per million (ppm) downfield of $CFCl_3$, using fluorobenzene as internal standard (C_6H_5F at –113.2 ppm). High-resolution mass spectra were recorded using electrospray ionisation (ES), electron impact ionisation (EI) or atmospheric solids analysis probe (ASAP) techniques on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer or a Thermofisher LTQ Orbitrap XL spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales,

Swansea or using electron impact ionisation on a Finnigan MAT 900 spectrometer at the University of Edinburgh. Low-resolution mass spectra were recorded using electron impact ionisation on an Agilent 7890A GC fitted with a 5975C MS detector. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Chiral HPLC analysis was performed on an Agilent 1100 instrument using 4.6 x 250 mm columns. Chiral GC analysis was performed on an Agilent 7890A instrument.

Preparation of α,β-Unsaturated Ketone Substrates

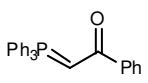
General Procedure A: Preparation of Phosphonium Ylides from Bromoketones and Bromoesters[104]



155 **132**

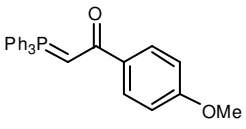
A solution of the appropriate 2-bromoester or 2-bromoketone (1.0 equiv) in toluene (1.3 M solution) was added dropwise over 10 min to a solution of triphenylphosphine (1.0 equiv) in toluene (1.3 M solution). The reaction mixture was stirred at room temperature for 18 h, and the resulting phosphonium salt was filtered and oven-dried. The phosphonium salt was used without further purification.

Na_2CO_3 (1.5 equiv) was added to a suspension of the phosphonium salt in H_2O and CH_2Cl_2 (1:1, 0.17 M with respect to phosphonium salt). The mixture was stirred at room temperature for 18 h and then transferred to a separating funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave the ylide, which was used without further purification.



1-Phenyl-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one (132a)[105]

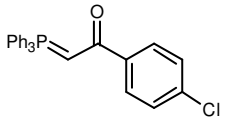
The title compound was prepared according to General Procedure A from 2-bromoacetophenone (3.98 g, 20.0 mmol) and the resultant ylide (5.80 g, 76%) displayed spectral data consistent with those described previously.[105]



1-(4-Methoxyphenyl)-2-(triphenyl-λ^5-phosphanylidene)ethanone (132b)[106]

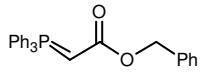
The title compound was prepared according to General Procedure A

from 2-bromo-4'-methoxyacetophenone (4.58 g, 20.0 mmol) and the resultant ylide (6.38 g, 78%) displayed spectral data consistent with those described previously.[106]



1-(4-Chlorophenyl)-2-(triphenyl-λ^5-phosphanylidene)ethanone (132c)[107]

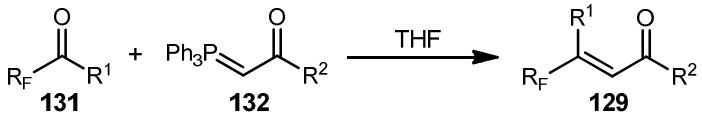
The title compound was prepared according to General Procedure A from 2-bromo-4'-chloroacetophenone (4.70 g, 20.0 mmol) and the resultant ylide (6.31 g, 76%) displayed spectral data consistent with those described previously.[107]



Benzyl 2-(triphenyl-λ^5-phosphoranylidene)acetate (132d)[108]

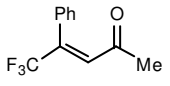
The title compound was prepared according to General Procedure A from benzyl bromoacetate (6.2 mL, 40 mmol) and the resultant ylide (15.28 g, 93%) displayed spectral data was consistent with those described previously.[108]

General Procedure B: Wittig Reaction of Trifluoromethyl Ketones



131 **132** **129**

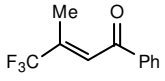
The appropriate perfluoroalkyl ketone (1.0 equiv) was added in one portion to a solution of the appropriate ylid (1.1 equiv) in THF (0.2 M solution) and the reaction mixture was heated under reflux until complete consumption of the ketone as observed by TLC analysis, or until no further reaction progress could be seen. The reaction mixture was concentrated *in vacuo* and the residue was triturated thoroughly with hexane. After removal of the hexane *in vacuo*, purification of the residue by column chromatography gave the *α*,*β*-unsaturated carbonyl compound.



(*E*)-4-Trifluoromethyl-4-phenyl-3-buten-2-one (129a)[57]

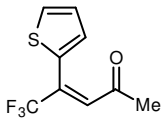
The title compound was prepared according to General Procedure B from (acetylmethylene)triphenylphosphorane (5.30 g, 16.5 mmol) and trifluoroacetophenone (2.1 mL, 15 mmol) for 6 hours and purified by column chromatography eluting with 10% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a >19:1 *E*:*Z* ratio of isomers) as a yellow oil (2.76 g, 92%). Spectral data was found to be consistent with that previously reported.[57] R_f = 0.52 (20% EtOAc/hexane); IR ($CDCl_3$) 3350, 1711 (C=O), 1683, 1359, 1282, 1240, 1174, 1130, 1027, 707 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31-

7.22 (3H, m, Ar**H**), 7.16-7.12 (2H, m, Ar**H**), 6.56 (1H, q, *J* = 1.4 Hz, C=C**H**), 1.73 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 199.2 (C), 139.0 (C, q, *J* = 30.9 Hz), 132.5 (CH, q, *J* = 4.9 Hz), 130.7 (C), 129.9 (CH), 129.0 (2 x CH_2), 128.7 (2 x CH_2), 122.8 (C, q, *J* = 274.8 Hz), 30.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –64.3 (3F, s).



(2*E*)-4,4,4-Trifluoro-3-methyl-1-phenylbut-2-en-1-one (129b)[109]

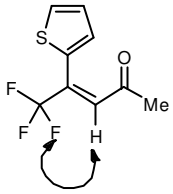
The title compound was prepared according to General Procedure B from **132a** (4.20 g, 11 mmol) and trifluoroacetone (0.90 mL, 10 mmol) for 15 hours and purified by column chromatography eluting with 10% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a >19:1 *E*:*Z* ratio of isomers) as a yellow oil (1.15 g, 54%). Spectral data was found to be consistent with that previously reported.[109] R_f = 0.50 (20% EtOAc/hexane); IR ($CDCl_3$) 3064, 2929, 1680 (C=O), 1598, 1316, 1295, 1232, 1180, 1128, 706 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.65-7.60 (1H, m, Ar**H**), 7.54-7.49 (2H, m, Ar**H**), 7.25-7.23 (1H, m, C=C**H**), 2.16 (3H, d, *J* = 1.5 Hz, C**H**$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 191.1 (C), 139.2 (C, q, *J* = 30.3 Hz), 137.1 (C), 133.8 (CH), 128.9 (2 x CH), 128.5 (2 x CH), 125.7 (CH, q, *J* = 5.3 Hz, C=C**H**), 123.4 (C, q, *J* = 274.0 Hz), 12.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –65.4 (3F, s).

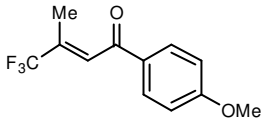


(3*Z*)-5,5,5-Trifluoro-4-(thiophen-2-yl)pent-3-en-2-one (129c)

The title compound was prepared according to General Procedure B from (acetylmethylene)triphenylphosphorane (245 mg, 0.8 mmol) and 2-(trifluoroacetyl)thiophene (90 μL, 0.7 mmol) for 3 hours and purified by column chromatography eluting with 5% EtOAc/hexane to give the major *Z*-isomer (the unpurified mixture contained a 14:1 *Z*:*E* ratio of isomers) as a yellow oil (140 mg, 91%). R_f = 0.43 (20% EtOAc/hexane); IR ($CDCl_3$) 3109, 1706 (C=O), 1632, 1432, 1357, 1329, 1138, 1046, 851, 704 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.52 (1H, dd, *J* = 5.1, 1.1 Hz, Ar**H**), 7.21 (1H, d, *J* = 3.6 Hz, Ar**H**), 7.10 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 6.71 (1H, q, *J* = 1.1 Hz, C=C**H**), 2.09 (3H, s, C**H**$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 199.7 (C), 132.7 (CH, q, *J* = 4.6 Hz), 131.2 (C, q, *J* = 32.3 Hz), 131.2 (CH), 129.9 (C), 129.5 (CH), 127.6 (CH), 122.3 (C, q, *J* = 275.1 Hz), 30.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.3 (3F, s); HRMS (EI) Exact mass calcd for $C_9H_6F_3OS$ $[M-H]^+$: 219.0086, found: 219.0086.

Determination of the alkene stereochemistry was acheived using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *Z* isomer:

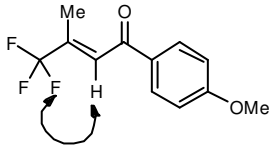


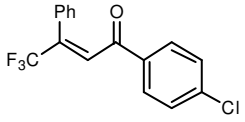


(2*E*)-4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-methylbut-2-en-1-one (129d)

The title compound was prepared according to General Procedure B from **132b** (4.51 g, 11 mmol) and trifluoroacetone (0.90 mL, 10 mmol) for 3 hours and purified by column chromatography eluting with 10% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a 12:1 *E*:*Z* ratio of isomers) as a yellow oil (1.16 g, 48%). R_f = 0.33 (20% EtOAc/hexane); IR ($CDCl_3$) 2939, 2844, 1674 (C=O), 1641, 1513, 1294, 1175, 1126, 1096, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91-7.95 (2H, m, Ar**H**), 7.19 (1H, m, C=C**H**), 6.96-7.00 (2H, m, Ar**H**), 3.90 (3H, s, OC**H**$_3$), 2.13 (3H, d, *J* = 1.3 Hz, C=CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 189.7 (C), 164.1 (C), 137.9 (C, q, *J* = 30.3 Hz), 131.0 (2 x CH), 130.2 (C), 126.2 (CH, q, *J* = 5.4 Hz), 123.5 (C, q, J = 274.0 Hz), 114.0 (2 x CH), 55.5 (CH_3), 12.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.9 (3F, s); HRMS (ES) Exact mass calcd for $C_{12}H_{12}F_3O_2$ $[M+H]^+$: 245.0784, found: 245.0787.

Determination of the alkene stereochemistry was acheived using a ^1H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:

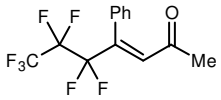




(2*E*)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-phenyl-but-2-en-1-one (129e)[110]

The title compound was prepared according to General Procedure B from **132c** (5.48 g, 13.2 mmol) and trifluoroacetophenone (1.70 mL, 12 mmol) for 6 hours and purified by column chromatography eluting with 2% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a >19:1 *E*:*Z* ratio of isomers) as a yellow oil (3.06 g, 82%). Spectral data was found to be consistent with that previously reported.[110] R_f = 0.57 (20% EtOAc/hexane); IR (neat) 1668 (C=O), 1585, 1273, 1171, 1126, 1090, 1011, 968, 843,

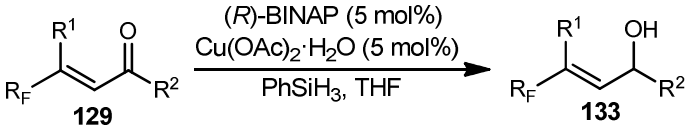
775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76-7.73 (2H, m, Ar**H**), 7.37-7.35 (2H, m, Ar**H**), 7.33-7.24 (5H, m, Ar**H**), 7.22 (1H, q, *J* = 1.4 Hz, C=C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.0 (C), 140.4 (C), 139.3 (C, q, *J* = 30.9 Hz), 134.3 (C), 130.6 (C), 130.2 (CH, q, *J* = 5.3 Hz), 130.2 (2 x CH), 129.6 (CH), 129.03 (2 x CH), 128.96 (2 x CH), 128.4 (2 x CH), 122.7 (C, q, *J* = 274.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.4 (3F, s).



(3*E*)-5,5,6,6,7,7,7-heptafluoro-4-phenylhept-3-en-2-one(129f)[57]

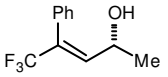
The title compound was prepared according to General Procedure B from (acetylmethylene)triphenylphosphorane (2.80 g, 8.8 mmol) and heptafluorobutyrophenone (1.50 mL, 8 mmol) for 4 hours and purified by column chromatography eluting with 10% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a >19:1 *E*:*Z* ratio of isomers) as a yellow oil (2.16 g, 86%). Spectral data was found to be consistent with that previously reported.[57] R_f = 0.54 (20% EtOAc/hexane); IR (neat) 1692 (C=O), 1342, 1227, 1180, 1159, 1115, 968, 743, 723, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.40 (3H, m, Ar**H**), 7.29 (2H, d, *J* = 7.4 Hz, Ar**H**), 6.72 (1H, s, C=C**H**), 1.86 (3H, m, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 199.2 (C), 138.3 (C, t, *J* = 21.8 Hz), 136.2 (CH, t, *J* = 7.7 Hz), 131.1 (C), 129.8 (CH), 129.5 (2 x CH), 128.6 (2 x CH), 117.7 (C, qt, *J* = 288.5, 34.1 Hz), 114.1 (C, tt, *J* = 257.9, 31.4 Hz), 109.0 (C, tqt, *J* = 266.5, 38.2, 38.1 Hz), 30.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, *J* = 10.4 Hz), −112.1 (2F, q, *J* = 10.4 Hz), −124.3 (2F, app s).

General Procedure C: Enantioselective Reduction of *α,β*-Unsaturated Ketones



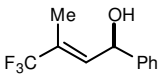
A solution of the appropriate ketone (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol) and (*R*)-BINAP (15.3 mg, 0.025 mmol) in THF (3 mL) was stirred at 0°C for 15 minutes. $PhSiH_3$ (93 μL, 0.75 mmol) was then added dropwise. The mixture was then stirred at 0°C for 1 hour and then at room temperature until complete consumption of the carbonyl compound as observed by TLC analysis. HCl (1mL, 1M) was then added. After 1 hour, the reaction mixture was partitioned between saturated NH_4Cl solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 2) and the combined organic fractions were dried

($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired saturated ketone.



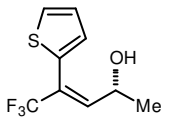
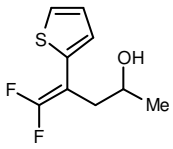
(*R*)-(3*E*)-5,5,5-Trifluoro-4-phenylpent-3-en-2-ol (133a)[57]

The title compound was prepared according to General Procedure C from **132a** (107 mg, 0.5 mmol) for 2 hours and purified by column chromatography eluting with 20% EtOAc/hexane to give **133a** as a yellow oil (73 mg, 68%). Spectral data was found to be consistent with that previously reported.[57] $[\alpha]_D^{24}$ +25.0 (*c* 0.64, $CHCl_3$); R_f = 0.36 (20% EtOAc/hexane); IR (neat) 3333 (OH), 1327, 1273, 1171, 1117, 1059, 899, 858, 775, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.41 (3H, m, Ar**H**), 7.27-7.25 (2H, m, Ar**H**), 6.39 (1H, dq, *J* = 8.9, 1.4 Hz, C=C**H**), 4.30-4.25 (1H, m, C**H**OH), 1.28 (3H, d, *J* = 6.4 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.6 (CH, q, *J* = 5.2 Hz), 131.5 (C), 131.2 (C, q, *J* = 30.2 Hz), 129.4 (2 x CH), 128.9 (CH), 128.5 (2 x CH), 123.1 (C, q, J = 273.4 Hz), 64.4 (CH), 23.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (major) = 19.6 min; t_r (minor) = 21.7 min, 63% ee.



(*R*)-(2*E*)-4,4,4-Trifluoromethyl-3-methyl-1-phenylbut-2-en-1-ol (133b)[111]

The title compound was prepared according to General Procedure C from **129b** (110 mg, 0.5 mmol) for 1.5 hours and purified by column chromatography eluting with 10% EtOAc/hexane to give **133b** as a yellow oil (75 mg, 68%). Spectral data was found to be consistent with that previously reported.[111] R_f = 0.45 (20% EtOAc/hexane); IR (neat) 3335 (OH), 1325, 1281, 1173, 1113, 1007, 997, 841, 762, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.35 (5H, m, Ar**H**), 6.33-6.30 (1H, dm, *J* = 7.9 Hz, C=C**H**), 5.50 (1H, d, *J* = 7.9 Hz, C**H**OH), 2.12 (1H, br, O**H**), 1.92 (3H, d, *J* = 1.3 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.7 (C), 134.3 (CH, q, *J* = 5.7 Hz), 128.9 (2 x CH), 128.3 (CH), 126.6 (C, q, *J* = 29.8 Hz), 126.0 (2 x CH), 123.8 (C, q, *J* = 272.9 Hz), 70.0 (CH), 11.1 (CH_3, q, *J* = 1.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.1 (3F, s); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (minor) = 23.9 min; t_r (major) = 26.2 min, 19% ee.

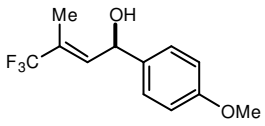



(*R*)-(3*Z*)-5,5,5-Trifluoro-4-(thiophen-2-yl)pent-3-en-2-ol (133c) and 5,5-difluoro-4-(thiophen-2-yl)pent-4-en-2-ol (134)

The title compounds were prepared according to General Procedure C from **129c** (110 mg, 0.5 mmol) for 16 hours and purified by column chromatography eluting with 5% EtOAc/hexane to give a yellow oil containing an inseparable mixture (3:1) of **133c** and **134** (61 mg, 55%).

133c: R_f = 0.24 (20% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, dd, *J* = 4.4, 1.9 Hz, Ar**H**), 7.10-7.08 (2H, m, Ar**H**), 6.46 (1H, dq, *J* = 8.9, 1.4 Hz, C=C**H**), 4.59 (1H, dq, *J* = 8.9, 6.5 Hz, C**H**OH), 1.63 (1H, br, O**H**), 1.36 (3H, d, *J* = 6.5 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.7 (CH, q, *J* = 4.9 Hz), 130.6 (C), 129.4 (CH), 127.6 (CH), 127.3 (CH), 124.4 (C, q, *J* = 31.4 Hz), 122.6 (C, q, *J* = 273.7 Hz), 64.5 (CH), 22.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.9 (3F, s); GC-MS (EI) *m/z* 222 (M^+, 4%), 202 (100%); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 210 nm); t_r (major) = 10.2 min; t_r (minor) = 12.0 min, 59% ee.

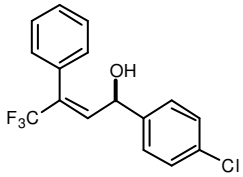
134: R_f = 0.24 (20% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (1H, dd, *J* = 5.2, 1.1 Hz, Ar**H**), 7.10-7.08 (1H, m, Ar**H**), 7.03 (1H, ddd, *J* = 4.9, 3.7, 1.0 Hz, Ar**H**), 4.03 (1H, ddq, *J* = 7.6, 6.2, 5.4 Hz, C**H**OH), 2.62 (1H, dddd, *J* = 14.5, 7.6, 2.8, 1.4 Hz, C**H**$_2$COH), 2.53 (1H, dddd, *J* = 14.5, 5.4, 2.8, 2.7 Hz, C**H**$_2$OH), 1.65 (1H, br, O**H**), 1.27 (3H, d, *J* = 6.2 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.5 (C, dd, *J* = 295.9, 288.8 Hz), 135.6 (C, dd, *J* = 6.8, 3.9 Hz), 127.1 (CH), 125.5 (CH, dd, *J* = 5.1, 5.1 Hz), 125.0 (CH, dd, *J* = 6.0, 2.8 Hz), 85.8 (C, dd, *J* = 26.1, 13.6 Hz), 66.5 (CH, dd, *J* = 2.6, 2.6 Hz), 37.5 (CH_2, d, *J* = 1.6 Hz), 23.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –83.5 (1F, d, *J* = 31.9 Hz), –89.7 (1F, d, *J* = 31.9 Hz); GC-MS (EI) *m/z* 204 (M^+, 63%), 159 (37%), 84 (100%).



(*R*)-(2*E*)-4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-methylbut-2-en-1-ol (133d)

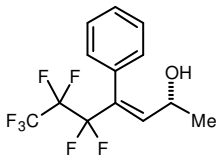
The title compound was prepared according to General Procedure C from **129d** (123 mg, 0.5 mmol) for 1.5 hours and purified by column chromatography eluting with 20% EtOAc/hexane to give **133d** as a yellow oil (22 mg, 18%). R_f = 0.17 (20% EtOAc/hexane); IR (neat) 3431 (OH), 1512, 1323, 1304, 1250, 1173, 1107, 1076, 1032, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (2H, m, Ar**H**), 6.93-6.90 (2H, m, Ar**H**), 6.32 (1H, dqq, *J* = 8.1, 1.5, 1.2 Hz, C=C**H**), 5.45 (1H, d, *J* = 8.1 Hz, C**H**OH), 3.82 (3H, s, OC**H**$_3$),

1.99 (1H, d, *J* = 3.3 Hz, O**H**), 1.88 (3H, d, *J* = 1.2 Hz, C=CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.6 (C), 134.6 (CH, q, *J* = 5.7 Hz), 133.9 (C), 127.4 (2 x CH), 126.1 (C, q, *J* = 29.8 Hz), 123.9 (C, q, J = 272.9 Hz), 114.3 (2 x CH), 69.7 (CH), 55.3 (CH_3), 11.1 (CH_3, q, *J* = 1.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.1 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{13}F_3O_2$ [M^+]: 246.08622, found: 246.08625. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 210 nm); t_r (minor) = 18.1 min; t_r (major) = 19.7 min, 4% ee.



(*R*)-(2*E*)-1-(4-chlorophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (133e)

The title compound was prepared according to General Procedure C from **129e** (160 mg, 0.5 mmol) for 1.5 hours and purified by column chromatography eluting with 10% EtOAc/hexane to give **133e** as a beige oil which solidified upon standing to an off-white amorphous solid (146 g, 91%). R_f = 0.37 (20% EtOAc/hexane); IR (neat) 3337 (OH), 1489, 1306, 1275, 1171, 1121, 1092, 1013, 831, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (3H, m, Ar**H**), 7.34-7.32 (2H, m, Ar**H**), 7.27-7.25 (2H, m, Ar**H**), 7.20-7.18 (2H, m, Ar**H**), 6.55 (1H, dq, *J* = 9.1, 1.4 Hz, C=C**H**), 5.12 (1H, dd, *J* = 9.1, 2.8 Hz, C**H**OH), 1.99 (1H, d, *J* = 2.8 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 139.9 (C), 136.1 (CH, q, *J* = 5.3 Hz), 134.1 (C), 132.5 (C, q, *J* = 30.5 Hz), 131.1 (C), 129.5 (2 x CH), 129.2 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 127.5 (2 x CH), 122.9 (C, q, *J* = 273.6 Hz), 69.8 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.4 (3F, s); HRMS (CI) Exact mass calcd for $C_{16}H_{11}F_3OCl$ [M–H]$^+$: 311.0445, found: 311.0444. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (major) = 40.2 min; t_r (minor) = 51.1 min, 25% ee.



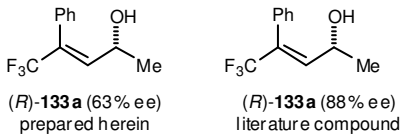
(*R*)-(3*E*)-5,5,6,6,7,7,7-heptafluoro-4-phenylhept-3-en-2-ol (133f)[57]

The title compound was prepared according to General Procedure C from **129f** (158 mg, 0.5 mmol) for 1.5 hours and purified by column chromatography eluting with 10% EtOAc/hexane to give **133f** as a white solid (125 g, 79%). Spectral data was found to be consistent with that previously reported.[57] $[\alpha]_D^{24}$ +2.3 (*c* 0.84, $CHCl_3$); m.p. 56-57 °C; R_f = 0.29 (20% EtOAc/hexane); IR (neat) 3298 (OH), 1346, 1221, 1202, 1180, 1161, 1111, 1099, 976, 718 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.39 (3H, m, Ar**H**), 7.23-7.22 (2H, m, Ar**H**), 6.40 (1H, dt, *J* = 8.9, 2.0 Hz, C=C**H**), 4.27-4.20 (1H, m,

C**H**OH), 1.63 (1H, br, O**H**), 1.27 (3H, d, *J* = 6.4 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 142.5 (CH, t, J = 8.0 Hz), 131.7 (C), 130.5 (C, t, J = 21.5 Hz), 129.9 (2 x CH), 128.8 (CH), 128.4 (2 x CH), 117.9 (C, qt, *J* = 288.3, 34.4 Hz), 114.1 (C, tt, *J* = 256.3, 31.0 Hz), 109.2 (C, tq, *J* = 291.1, 37.7 Hz), 64.6 (CH), 22.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, *J* = 10.2 Hz), –111.0 (2F, dq, *J* = 25.9, 10.2 Hz), –124.5 (2F, br); Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99:1 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (major) = 12.0 min; t_r (minor) = 15.7 min, 41% ee.

Stereochemical Determinations

The absolute stereochemistry of **133a** was assigned as (*R*) by comparison of the direction of optical rotation with that reported in the literature.[57]



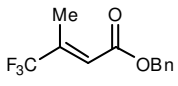
(*R*)-**133a**: $[\alpha]_D^{24}$ +25.0 (*c* 0.64, $CHCl_3$) Herein

(*R*)-**133a**: $[\alpha]_D^{20}$ +6.4 (*c* 1.3, $CHCl_3$) Literature

The absolute stereochemistry of **133e** was assigned as (*R*) by comparison of the HPLC trace to that of **255d** (**Chapter 5**). In both cases the major product eluted first, suggesting that **133e** was the (*R*) isomer.

The absolute stereochemistries of the remaining products **133b**,**c**,**d** and **f** were assigned by analogy.

Preparation of *α*,*β*-Unsaturated Ester Substrates

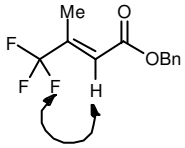


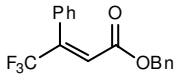
(*E*)-4,4,4-Trifluoro-3-methyl-but-2-enoic acid benzyl ester (145a)

The title compound was prepared according to General Procedure B from **132d** (4.51 g, 11 mmol) and trifluoroacetone (0.90 mL, 10 mmol) for 2.5 hours and purified by column chromatography eluting with 5% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a 19:1 *E*:*Z* ratio of isomers) as a colourless oil (2.10 g, 86%). R_f = 0.68 (20% EtOAc/hexane); IR ($CDCl_3$) 3056, 2958, 1731 (C=O), 1359, 1297, 1258, 1194, 1131, 1099, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.35 (5H, m, Ar**H**), 6.39 (1H, m, =C**H**), 5.23 (2H, s, C**H**$_2$Ph), 2.28 (3H, d, *J* = 1.6 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.6 (C), 142.6 (C, q, *J* = 30.4 Hz), 135.3 (C), 128.7 (2 x CH), 128.5 (CH), 128.4 (2 x CH),

123.1 (C, q, *J* = 274.4 Hz), 121.2 (CH, q, J = 5.8 Hz), 66.7 (CH_2), 12.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.3 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{11}F_3O_2$ $[M]^+$: 244.0706, found: 244.0704.

Determination of the alkene stereochemistry was acheived using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:

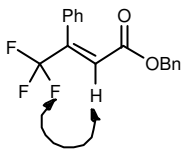


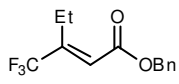


(*E*)-4,4,4-Trifluoro-3-phenyl-but-2-enoic acid benzyl ester (145b)

The title compound was prepared according to General Procedure B from **132d** (4.51 g, 11 mmol) and trifluoroacetophenone (1.4 mL, 10 mmol) for 2 hours and purified by column chromatography eluting with 5% EtOAc/5% toluene/90% hexane to give the major *E*-isomer (the unpurified mixture contained a 11:1 *E*:*Z* ratio of isomers) as a pale yellow oil (1.83 g, 60%). R_f = 0.59 (20% EtOAc/hexane); IR ($CDCl_3$) 3065, 3035, 1735 (C=O), 1284, 1259, 1179, 1133, 1005, 749, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, tt, *J* = 7.5, 1.0 Hz, Ar**H**), 7.37 (2H, tt, *J* = 7.5, 2.0 Hz, Ar**H**), 7.31-7.26 (5H, m, Ar**H**), 7.11-7.09 (2H, m, Ar**H**), 6.65 (1H, q, *J* = 1.0 Hz, =C**H**), 5.03 (2H, s, C**H**$_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.0 (C), 142.7 (C, q, *J* = 30.9 Hz), 135.3 (C), 130.8 (C), 129.4 (CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (CH), 128.31 (2 x CH), 128.26 (2 x CH), 124.2 (CH, q, J = 5.5 Hz), 122.4 (C, q, *J* = 275.0 Hz), 66.9 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.8 (3F, s). HRMS (ES) Exact mass calcd for $C_{17}H_{17}NF_3O_2$ $[M + NH_4]^+$: 324.1206, found: 324.1207.

Determination of the alkene stereochemistry was acheived using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:



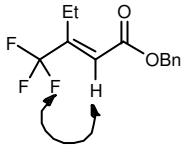


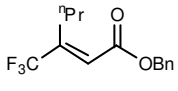
(*E*)-3-Trifluoromethyl-pent-2-enoic acid benzyl ester (145c)

The title compound was prepared according to General Procedure B from **132d** (2.23 g, 5.5 mmol) and 1,1,1-trifluorobutanone (680 μL, 5 mmol) for 5.5 hours and purified by column chromatography eluting with 2% EtOAc/hexane to give the major *E*-

isomer (the unpurified mixture contained a 9:1 *E*:*Z* ratio of isomers) as a colourless oil (0.78 g, 60%). R_f = 0.75 (20% EtOAc/hexane); IR (film) 1731 (C=O), 1456, 1309, 1257, 1191, 1130, 1115, 1040, 746, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.35 (5H, m, Ar**H**), 6.37 (1H, s, =C**H**), 5.23 (2H, s, C**H**$_2$Ph), 2.72 (2H, q, *J* = 7.4 Hz, C**H**$_2$CH$_3$), 1.19 (3H, t, *J* = 7.4 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.3 (C), 148.3 (C, q, *J* = 28.7 Hz), 135.3 (C), 128.7 (2 x CH), 128.5 (CH), 128.4 (2 x CH), 123.5 (C, q, *J* = 275.3 Hz), 121.3 (CH, q, *J* = 6.1 Hz), 66.7 (CH$_2$), 20.3 (CH$_2$), 13.3 (CH$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.3 (3F, s). HRMS (EI) Exact mass calcd for $C_{13}H_{13}F_3O_2$ $[M]^+$: 258.0862, found: 258.0864.

Determination of the alkene stereochemistry was acheived using a ^1H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:

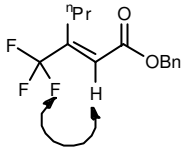


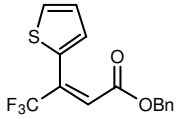


(*E*)-3-Trifluoromethyl-hex-2-enoic acid benzyl ester (145d)

The title compound was prepared according to General Procedure B from **132d** (2.23 g, 5.5 mmol) and 1,1,1-trifluoropentanone (700 μL, 5 mmol) for 5.5 hours and purified by column chromatography eluting with 2% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a 13:1 *E*:*Z* ratio of isomers) as a colourless oil (0.84 g, 62%). R_f = 0.58 (20% EtOAc/hexane); IR (film) 2967, 1732 (C=O), 1456, 1315, 1295, 1261, 1236, 1190, 1121, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.36 (5H, m, *J* = 2.4 Hz, Ar**H**), 6.37 (1H, app d, *J* = 0.9 Hz, =C**H**), 5.22 (2H, s, C**H**$_2$Ph), 2.66-2.63 (2H, m, C**H**$_2$CH$_2$CH$_3$), 1.58 (2H, tq, *J* = 7.5, 7.4 Hz, CH$_2$C**H**$_2$CH$_3$), 0.96 (3H, t, *J* = 7.4 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.4 (C), 146.8 (C, q, *J* = 28.9 Hz), 135.2 (C), 128.7 (2 x CH), 128.5 (CH), 128.4 (2 x CH), 123.4 (C, q, *J* = 275.0 Hz), 121.7 (CH, q, *J* = 6.2 Hz), 66.7 (CH$_2$), 28.7 (CH$_2$), 22.3 (CH$_2$), 14.1 (CH$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.1 (3F, s). HRMS (CI) Exact mass calcd for $C_{14}H_{19}F_3O_2N$ $[M + NH_4]^+$: 290.1362, found 290.1361.

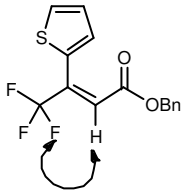
Determination of the alkene stereochemistry was acheived using a ^1H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:

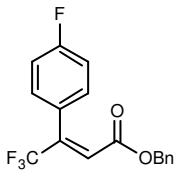




(*Z*)-4,4,4-Trifluoro-3-thiophen-2-yl-but-2-enoic acid benzyl ester (145e)

The title compound was prepared according to General Procedure B from **132d** (1.24 g, 3.9 mmol) and 2-(trifluoroacetyl)thiophene (450 μL, 3.5 mmol) for 16 hours and purified by column chromatography eluting with 5% EtOAc/5% toluene/90 % hexane to give the major *Z*-isomer (the unpurified mixture contained a 10:1 *Z*:*E* ratio of isomers) as a yellow oil (0.78 g, 72%). R_f = 0.42 (10% EtOAc/hexane); IR (film) 3067, 3034, 1735 (C=O), 1456, 1366, 1334, 1282, 1184, 1137, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dt, *J* = 5.1, 1.2 Hz, Ar**H**), 7.32-7.36 (3H, m, Ar**H**), 7.23-7.22 (3H, m, Ar**H**), 7.04 (1H, ddd, *J* = 5.1, 3.7, 1.3 Hz, Ar**H**), 6.64 (1H, app s, =C**H**), 5.15 (2H, s, C$\mathbf{H}_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.7 (C), 134.8 (C), 134.7 (C, q, *J* = 31.7 Hz), 130.5 (CH), 129.8 (C), 128.8 (CH), 128.55 (2 x CH), 128.49 (CH), 128.5 (2 x CH), 127.1 (CH), 125.1 (C, q, *J* = 277.0 Hz), 124.1 (CH, q, *J* = 5.4 Hz), 67.2 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.6 (3F, s). HMRS (ES) Exact mass calcd for $C_{15}H_{15}NF_3O_2S$ $[M + NH_4]^+$: 330.0770, found: 330.0772. Determination of the alkene stereochemistry was acheived using a ^1H–^{19}F HOESY experiment which showed the following diagnostic peak for the *Z* isomer:



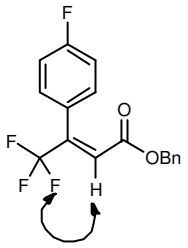


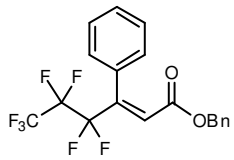
(*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)-but-2-enoic acid benzyl ester (145f)

The title compound was prepared according to General Procedure B from **132d** (2.26 g, 5.5 mmol) and 4-fluoro-*α*,*α*,*α*-acetophenone (700 μL, 5 mmol) for 3 hours and purified by column chromatography eluting with 0→5% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained a 12:1 *E*:*Z* ratio of isomers) as a colourless oil (1.00 g, 62%). R_f = 0.55 (20% EtOAc/hexane); IR (neat) 1736 (C=O), 1512, 1285, 1256, 1236, 1180, 1157, 1132, 841, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.31 (3H, m, Ar**H**), 7.24 (2H, dd, *J* = 7.5, 5.6 Hz, Ar**H**), 7.17-7.14 (2H, m, Ar**H**), 7.03 (2H, t, *J* = 8.5 Hz, Ar**H**), 6.67 (1H, s, =C**H**), 5.06 (2H, s, C$\mathbf{H}_2$Ar); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.3 (C), 163.3 (C, d, *J* = 249.6 Hz), 141.7 (C, q, *J* = 30.6 Hz), 134.7 (C), 130.7 (2 x CH, d, *J* = 8.4 Hz), 128.53 (2 x CH), 128.47 (2 x CH), 128.3 (CH), 126.6 (C), 124.7 (CH, q, *J* = 5.1

Hz), 122.3 (C, q, J = 275.3 Hz), 115.5 (2 x CH, d, J = 21.9 Hz), 67.1 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.8 (3F, s), –111.5 (1F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{12}F_4O_2$ $[M]^+$: 324.0768, found: 324.0768.

Determination of the alkene stereochemistry was acheived using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:

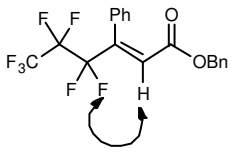


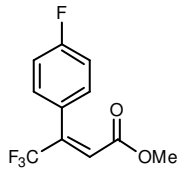


(*E*)-4,4,5,5,6,6,6-Heptafluoro-3-phenyl-hex-2-enoic acid benzyl ester (145g)

The title compound was prepared according to General Procedure B from **132d** (2.23 g, 5.5 mmol) and heptafluoropropyl phenyl ketone (930 μL, 5 mmol) for 4 hours and purified by column chromatography eluting with 1% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained an 11:1 *E*:*Z* ratio of isomers) as a colourless oil (1.35 g, 67%). R_f = 0.64 (20% EtOAc/hexane); IR (film) 1739 (C=O), 1497, 1457, 1342, 1231, 1117, 1006, 908, 746, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, tt, J = 7.0, 1.5 Hz, Ar**H**), 7.39-7.35 (2H, m, Ar**H**), 7.34-7.31 (3H, m, Ar**H**), 7.27-7.26 (2H, m, Ar**H**), 7.13-7.11 (2H, m, Ar**H**), 6.69-6.67 (1H, m ,=C**H**), 5.03 (2H, s, C**H**$_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.8 (C), 142.2 (C, t, J = 21.7 Hz), 134.7 (C), 131.1 (C), 129.3 (CH), 129.0 (2 x CH), 128.5 (2 x CH), 128.40 (CH), 128.38 (2 x CH), 128.1 (2 x CH), 127.7 (CH, t, J = 8.8 Hz), 117.7 (C, qt, J = 288.4, 36.3 Hz), 114.0 (C, tt, J = 258.3, 34.9 Hz), 108.9 (C, tqt, J = 266.6, 36.3, 34.9 Hz), 67.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, J = 10.2 Hz), –112.0 (2F, q, J = 10.2 Hz), –124.2 (2F, br s). HMRS (ES) Exact mass calcd for $C_{19}H_{17}NF_7O_2$ $[M + NH_4]^+$: 424.1142, found: 424.1143.

Determination of the alkene stereochemistry was acheived using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:

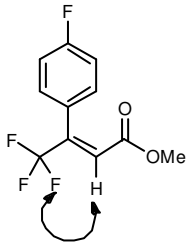


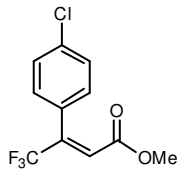


(*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)-but-2-enoic acid methyl ester (145h)[112]

The title compound was prepared according to General Procedure B from methyl (triphenylphosphoranylidene)acetate (1.84 g, 5.5 mmol) and 4-fluoro-α,α,α-acetophenone (700 μL, 5 mmol) for 3 hours and purified by column chromatography eluting with 5% EtOAc/hexane to give the major *E*-isomer (the unpurified mixture contained an 11:1 *E*:*Z* ratio of isomers) as a colourless oil (0.86 g, 69%). Spectral data was found to be consistent with that previously reported.[112] R_f = 0.56 (20% EtOAc/hexane); IR (film) 1741 (C=O), 1607, 1513, 1288, 1261, 1213, 1183, 1160, 1134, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.35 (2H, m, Ar**H**), 7.22-7.17 (2H, m, Ar**H**), 6.72 (1H, q, *J* = 1.0 Hz, =C**H**), 3.72 (3H, s, $CO_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.3 (C), 163.3 (C, d, *J* = 249.4 Hz), 142.0 (C, q, *J* = 31.1 Hz), 130.6 (2 x CH, d, *J* = 8.5 Hz), 126.6 (C, d, *J* = 3.6 Hz), 124.3 (CH, q, *J* = 5.4 Hz), 122.3 (C, q, *J* = 274.8 Hz), 115.5 (2 x CH, d, *J* = 21.9 Hz), 52.1 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.8 (3F, s), –111.5 (1F, s). HRMS (CI) Exact mass calcd for $C_{11}H_9F_4O_2$ $[M + H]^+$: 249.0533, found 249.0532.

Determination of the alkene stereochemistry was acheived using a ^1H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:



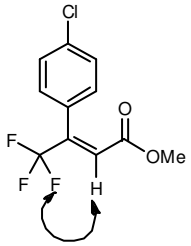


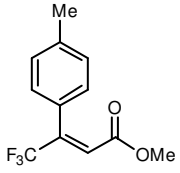
(*E*)-3-(4-Chlorophenyl)-4,4,4-trifluoro-but-2-enoic acid methyl ester (145i)

The title compound was prepared according to General Procedure B from methyl (triphenylphosphoranylidene)acetate (1.10 g, 3.3 mmol) and 4'-chloro-2,2,2-trifluoroacetophenone (0.63 g, 3 mmol) for 3 hours and purified by column chromatography eluting with 5% EtOAc/5% toluene/90% hexane to give the major *E*-isomer (the unpurified mixture contained a 12:1 *E*:*Z* ratio of isomers) as a pale yellow oil (0.42 g, 53%). R_f = 0.65 (20% EtOAc/hexane); IR (film) 2955, 2929, 1778, 1739 (C=O), 1494, 1286, 1259, 1213, 1187, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, t, *J* = 2.4 Hz, Ar**H**),

7.39 (1H, t, *J* = 2.4 Hz, Ar**H**), 7.25 (1H, app s, Ar**H**), 7.23 (1H, app s, Ar**H**), 6.63 (1H, q, *J* = 1.3 Hz, =C**H**), 3.65 (3H, s, $CO_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.2 (C), 142.0 (C, q, *J* = 31.1 Hz), 135.7 (C), 130.0 (2 x CH), 129.1 (C), 128.6 (2 x CH), 124.4 (CH, q, *J* = 4.3 Hz), 122.2 (C, q, *J* = 220.7 Hz), 52.1 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.7 (3F, s). HMRS (CI) Exact mass calcd for $C_{11}H_{11}NF_3O_2Cl$ $[M\text{-}H+NH_4]^+$: 281.0425, found: 281.0425.

Determination of the alkene stereochemistry was acheived using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:

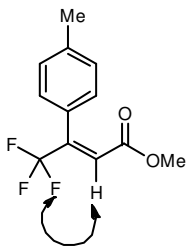


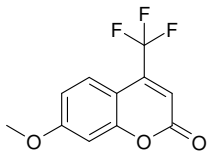


(*E*)-4,4,4-Trifluoro-3-*p*-tolyl-but-2-enoic acid methyl ester (145j)

The title compound was prepared according to General Procedure B from methyl (triphenylphosphoranylidene)acetate (1.84 g, 5.5 mmol) and 4-(trifluoroacetyl)toluene (760 μL, 5 mmol) for 4 hours and purified by column chromatography eluting with 30% CH_2Cl_2/hexane to give the major *E*-isomer (the unpurified mixture contained a 7:1 *E*:*Z* ratio of isomers) as a colourless oil (1.22 g, 77 %). R_f = 0.59 (20% EtOAc/hexane); IR (film) 1741 (C=O), 1515, 1285, 1259, 1207, 1182, 1133, 1011, 980, 662 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.19 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.60 (1H, q, *J* = 1.5 Hz, =C**H**), 3.64 (3H, s, $CO_2C\mathbf{H}_3$), 2.40 (3H, s, $ArC\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.6 (C), 143.1 (C, q, *J* = 30.8 Hz), 139.5 (C), 129.0 (2 x CH), 128.4 (2 x CH), 127.8 (C), 122.5 (C, q, *J* = 274.8 Hz), 123.5 (CH, q, *J* = 5.4 Hz), 52.0 (CH_3), 21.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{11}F_3O_2$ $[M]^+$: 244.0706, found: 244.0706.

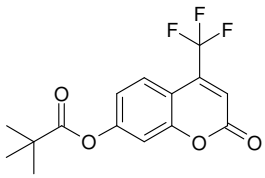
Determination of the alkene stereochemistry was acheived using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E* isomer:





7-Methoxy-4-(trifluoromethyl)-2H-chromen-2-one (145k)

To a microwave vial containing 3-methoxyphenol (0.55 mL, 5 mmol) and ethyl-4,4,4-trifluoroacetoacetate (0.73 mL, 5 mmol) was added trifluoroacetic acid (4mL). The mixture was heated under microwave irradiation for 30 minutes at 135 °C. The bright red reaction mixture was then poured onto ice water. The bright pink precipitate which formed was filtered off, dissolved in ethyl acetate, dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography eluting with 2 – 10% EtOAc/hexane afforded the desired product as white needles (0.46 g, 37%). R_f = 0.44 (20% EtOAc/hexane); m.p. 101-102 °C; IR (neat) 1726 (C=O), 1277, 1188, 1177, 1169, 1142, 1119, 874, 851, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (1H, dq, *J* = 9.0, 1.8 Hz, Ar**H**), 6.93 (1H, dd, *J* = 9.0, 2.5 Hz, Ar**H**), 6.89 (1H, d, *J* = 2.5 Hz, Ar**H**), 6.63 (1H, s, =C**H**), 3.91 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.5 (C), 159.4 (C), 156.4 (C), 141.6 (C, q, *J* = 32.8 Hz), 126.3 (CH, q, *J* = 2.3 Hz), 121.6 (C, q, *J* = 275.5 Hz), 113.4 (CH), 112.2 (CH, q, *J* = 5.8 Hz), 107.0 (C), 101.4 (CH), 55.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –64.8 (3F, s); HRMS (CI) Exact mass calcd for $C_{11}H_8O_3F_3$ $[M+H]^+$: 245.0420, found: 245.0415.



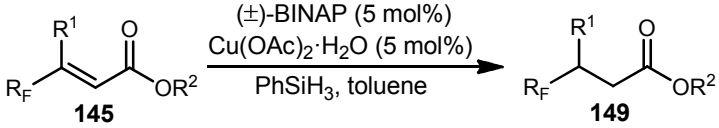
2-Oxo-4-(trifluoromethyl)-2H-chromen-7-yl-2,2-dimethylpropanoate (145l)

To a solution of 7-hydroxy-4-(trifluoromethyl)coumarin (0.58 g, 2.5 mmol) and 4-(dimethylamino)pyridine (30 mg, 0.25 mmol) in dichloromethane (20 mL) was added pyridine (0.22 mL, 2.75 mmol) and pivaloyl chloride (0.34 mL, 2.75 mmol). The mixture was allowed to stir at room temperature for 24 hours, then saturated $NaHCO_3$ solution (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20mL x 2). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid (0.71 g, 90%). R_f = 0.53 (20% EtOAc/hexane); m.p. 84-86 °C; IR (neat) 1749 (C=O), 1261, 1184, 1167, 1146, 1128, 1092, 908, 874, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.19 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.11 (1H, dd, *J* = 8.3, 2.0 Hz, Ar**H**), 6.78 (1H, s, =C**H**), 1.39 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.1 (C), 158.5 (C), 155.1 (C), 154.6 (C), 141.1 (C, q, *J* = 33.1 Hz), 126.2 (CH), 121.4 (C, q, *J* = 277.5 Hz), 119.0 (CH), 115.2 (CH, q, *J* = 5.6 Hz), 111.1 (C), 111.0 (CH), 39.3 (C), 27.0 (3 x CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –64.9

(3F, s). HRMS (ES) Exact mass calcd for $C_{15}H_{17}O_4F_3N$ $[M+NH_4]^+$: 332.1104, found: 332.1104.

Reductions of *α,β*-Unsaturated Esters

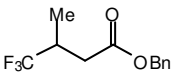
General Procedure D: Racemic Reduction of *α,β*-Unsaturated Esters.



A solution of the appropriate ester (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol), (±)-BINAP (15.3 mg, 0.025 mmol) in toluene (2 mL) was stirred at room temperature for 15 minutes before being cooled to 0 °C. $PhSiH_3$ (93 µL, 0.75 mmol) was then added dropwise. The mixture was then stirred at 0°C for 1 hour and then at room temperature until complete consumption of the carbonyl compound as observed by TLC analysis, or until no further reaction progress could be seen. HCl (1mL, 1M) was then added. After 1 hour, the reaction mixture was partitioned between saturated NH_4Cl solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 2) and the combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired saturated ester.

General Procedure E: Enantioselective Reduction of *α,β*-Unsaturated Esters.

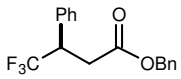
As for General Procedure D, but with $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol) and (*R*)-BINAP (9.3 mg, 0.015 mmol) employed as ligand.



Benzyl 4,4,4-trifluoro-3-methylbutanoate (149a)

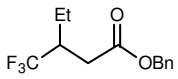
The title compound was prepared according to General Procedure D from **145a** (122 mg, 0.50 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a colourless oil (78 mg, 63%). R_f = 0.26 (30% CH_2Cl_2/hexane); IR (film) 1740 (C=O), 1304, 1287, 1269, 1238, 1177, 1128, 1020, 739, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.42 (5H, m, Ar**H**), 5.17 (2H, s, C**H**$_2$Ph), 2.78-2.84 (1H, m, C**H**CF_3), 2.75 (1H, dd, *J* = 16.4, 3.7 Hz, C**H**$_2$CO), 2.36 (1H, dd, *J* = 16.4, 9.4 Hz, C**H**$_2$CO), 1.18 (3H, d, J = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.6 (C), 135.5 (C), 128.7 (2 x CH), 128.4 (CH), 128.3 (2 x CH), 127.6 (C, q, *J* = 278.8 Hz), 66.8 (CH_2), 35.1 (CH, q, *J* =

29.1 Hz), 34.8 (CH_2, q, J = 2.6 Hz), 13.0 (CH_3, q, J = 2.8 Hz); ^{19}F NMR (235 MHz, $CDCl_3$) δ –74.0 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{13}F_3O_2$ [M^+]: 246.0862, found: 246.0862.



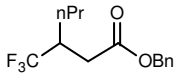
(*R*)-Benzyl 4,4,4-trifluoro-3-phenylbutanoate (149b)

The title compound was prepared according to General Procedure E from **145b** (153 mg, 0.50 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a colourless oil, which solidified upon standing to give a white solid (137 mg, 89%). $[\alpha]_D^{24}$ –16.6 (*c* 0.96, $CHCl_3$); R_f = 0.44 (20% EtOAc/hexane); m.p. 30-32 °C; IR ($CDCl_3$) 3583, 1727 (C=O), 1498, 1455, 1305, 1250, 1159, 1106, 752, 697cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.36 (8H, m, Ar**H**), 7.17-7.19 (2H, m, Ar**H**), 5.06 (1H, d, J = 12.3 Hz, C**H**$_2$Ph), 5.02 (1H, d, J = 12.3 Hz, C**H**$_2$Ph), 3.94 (1H, dqd, J = 9.6, 9.3, 5.0 Hz, CF_3C**H**), 3.09 (1H, dd, J = 16.2, 5.0 Hz, C**H**$_2$$CO_2$Bn), 2.98 (1H, dd, J = 16.2, 9.6 Hz, C**H**$_2$$CO_2$Bn); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.8 (C), 135.3 (C), 133.5 (C), 128.9 (2 x CH), 128.7 (2 x CH), 128.6 (CH), 128.5 (2 x CH), 128.3 (CH), 128.2 (2 x CH), 126.3 (C, q, J = 279.7 Hz), 66.8 (CH_2), 46.1 (CH, q, J = 27.8 Hz), 34.5 (CH_2, q, J = 2.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.4 (3F, s). HRMS (ES) Exact mass calcd for $C_{17}H_{19}NO_2F_3$ [M+NH_4]$^+$: 326.1362, found: 326.1363. Enantiomeric excess was determined by GC with a Cyclodex-B column (inlet T = 220°C, oven T = 220°C, 0.4 mL/min); t_r (major) = 9.8 min; t_r (minor) = 11.5 min, 99% ee.



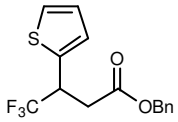
Benzyl 4,4,4-trifluoro-3-ethylbutanoate (149c)

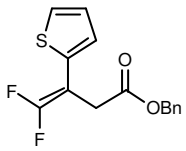
The title compound was prepared according to General Procedure D from **145c** (129 mg, 0.50 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a colourless oil (84 mg, 65%). R_f = 0.69 (20% EtOAc/hexane); IR (film) 2924, 1742 (C=O), 1690, 1271, 1256, 1231, 1175, 1128, 739, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.39 (5H, m, Ar**H**), 5.16 (2H, s, C**H**$_2$Ph), 2.64-2.73 (2H, m, C**H**CF_3 and C**H**$_2$C=O), 2.41-2.48 (1H, m, C**H**$_2$C=O), 1.74 (1H, dqd, J = 14.9, 7.4, 6.4 Hz, C**H**$_2$$CH_3$), 1.51 (1H, dqd, J = 14.9, 7.4, 6.4 Hz, C**H**$_2$$CH_3$), 0.99 (3H, td, J = 7.4, 0.9 Hz, CH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.9 (C), 135.5 (C), 128.9 (2 x CH), 128.4 (CH), 128.3 (2 x CH), 127.8 (C, q, J = 279.8 Hz), 66.8 (CH_2), 41.0 (CH, q, J = 26.0 Hz), 32.9 (CH_2, q, J = 2.7 Hz), 21.3 (CH_2, q, J = 2.3 Hz), 11.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.3 (3F, s); HRMS (EI) Exact mass calcd for $C_{13}H_{15}F_3O_2$ [M^+]: 260.1019, found: 260.1016.



Benzyl 3-(trifluoromethyl)hexanoate (149d)

The title compound was prepared according to General Procedure D from **145d** (136 mg, 0.50 mmol) and purified by column chromatography (1% EtOAc/hexane) to give a colourless oil (85 mg, 62%). R_f = 0.66 (20% EtOAc/hexane); IR (film) 2965, 1742 (C=O), 1258, 1231, 1175, 1113, 1051, 1013, 795, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.41 (5H, m, Ar**H**), 5.17 (2H, s, C**H**$_2$Ph), 2.78-2.70 (1H, m, C**H**CF_3), 2.67 (1H, dd, *J* = 16.3, 5.7 Hz, C**H**$_2$CO), 2.43 (1H, dd, *J* = 16.3, 7.4 Hz, C**H**$_2$CO), 1.61-1.69 (1H, m, C**H**$_2$CH$_2$), 1.37-1.43 (3H, m, C**H**$_2$C**H**$_2$), 0.92 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.0 (C), 135.5 (C), 128.6 (2 x CH), 128.4 (CH), 128.3 (2 x CH), 127.8 (C, q, *J* = 279.7 Hz), 66.8 (CH_2), 39.5 (CH, q, *J* = 26.3 Hz), 33.4 (CH_2, q, *J* = 2.8 Hz), 30.4 (CH_2, q, *J* = 2.0 Hz), 19.8 (CH_2), 13.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.5 (3F, s); HRMS (ES) Exact mass calcd for $C_{14}H_{21}F_3O_2N$ $[M+NH_4]^+$: 292.1524, found: 292.1511.





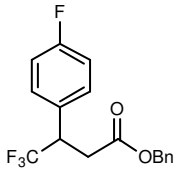
Benzyl 4,4,4-trifluoro-3-(thiophen-2-yl) butanoate (149e) and benzyl 4,4-difluoro-3-(thiophen-2-yl) but-3-enoate (150).

The title compounds were prepared according to General Procedure D from **145e** (156 mg, 0.50 mmol) and purified by column chromatography (1% EtOAc/hexane) to give a light brown oil containing an inseparable mixture of products **149e** and **150** (3.3:1, 53 mg, 34%).

149e: R_f = 0.26 (10% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (6H, m, Ar**H**), 6.98-7.06 (2H, m, Ar**H**), 5.11 (1H, d, *J* = 12.0 Hz, C**H**$_2$Ph), 5.07 (1H, d, *J* = 12.0 Hz, C**H**$_2$Ph), 4.27 (1H, qdd, *J* = 18.5, 10.0, 4.7 Hz, C**H**CF_3), 3.10 (1H, dd, *J* = 16.2, 4.7 Hz, C**H**$_2$CO), 2.95 (1H, dd, *J* = 16.2, 10.0 Hz, C**H**$_2$CO); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.5 (C), 135.2 (C), 128.6 (2 x CH), 128.4 (CH), 128.2 (2 x CH), 127.7 (CH), 127.1 (C), 126.9 (CH), 125.9 (CH), 125.5 (C, q, *J* = 280.2 Hz), 67.0 (CH_2), 41.7 (CH, q, *J* = 29.5 Hz), 35.7 (CH_2, q, *J* = 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.4 (3F, s); GC-MS (EI) *m/z* 314 (M^+, 7%), 294 (2%), 223 (10%), 165 (13%), 91 (100%).

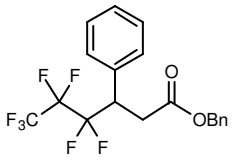
150: R_f = 0.26 (10% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (6H, m, Ar**H**), 6.98-7.06 (2H, m, Ar**H**), 5.17 (2H, s, C**H**$_2$Ph), 3.50 (2H, t, J = 2.0 Hz, C**H**$_2$CO); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.6 (C, dd, *J* = 4.1, 2.9 Hz), 154.7 (C, dd, *J* = 295.9, 290.1 Hz), 134.8 (C, dd, *J* = 7.2, 3.0 Hz), 128.5 (2 x CH), 128.3 (CH), 128.1 (2 x CH), 127.4 (CH), 126.6 (C), 125.4 (CH, dd, *J* = 5.8, 4.3 Hz), 125.3 (CH, dd, J = 6.7, 3.4 Hz), 83.7 (C, dd, *J* =

25.9, 18.3 Hz), 70.0 (CH_2), 33.6 (CH_2, d, J = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –83.0 (1F, d, J = 27.9 Hz), –89.1 (1F, d, J = 27.9 Hz); GC-MS (EI) *m/z* 314 (M^+, 1%), 91 (100%).



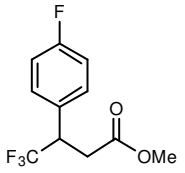
Benzyl 4,4,4-trifluoro-3-(4-fluorophenyl)butanoate (149f).

The title compound was prepared according to General Procedure D from **145f** (162 mg, 0.50 mmol) and purified by column chromatography (1% EtOAc/hexane) to give a colourless oil (124 mg, 76%). R_f = 0.44 (10% EtOAc/hexane); IR (film) 1738 (C=O), 1514, 1366, 1288, 1256, 1234, 1175, 1051, 841, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.41 (5H, m, Ar**H**), 7.18-7.19 (2H, m, Ar**H**), 7.05 (2H, dt, J = 8.7, 2.2 Hz, Ar**H**), 5.04-5.10 (2H, m, C**H**$_2$Ph), 3.95 (1H, qdd, J = 18.8, 9.8, 4.3 Hz, C**H**CF_3), 3.10 (1H, ddq, J = 16.1, 4.3, 3.9 Hz, C**H**$_2$CO), 2.95 (1H, ddq, J = 16.1, 9.8, 3.6 Hz, C**H**$_2$CO); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.6 (C), 162.7 (C, d, J = 247.7 Hz), 135.2 (C), 130.6 (2 x CH, d, J = 8.3 Hz), 129.2 (C, d, J = 1.4 Hz), 128.5 (2 x CH), 128.4 (CH), 128.2 (2 x CH), 126.1 (C, q, J = 279.5 Hz), 115.7 (2 x CH, d, J = 21.7 Hz), 66.9 (CH_2), 45.5 (CH, q, J = 28.1 Hz), 34.5 (CH_2, q, J = 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.7 (3F, s), –113.4 (1F, s); HRMS (ES) Exact mass calcd for $C_{17}H_{18}F_4O_2N$ $[M+NH_4]^+$: 344.1268, found: 344.1267.



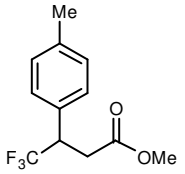
4,4,5,5,6,6,6-Heptafluoro-3-phenylhexanoic acid benzyl ester (149g)

The title compound was prepared according to General Procedure D from **145g** (203 mg, 0.50 mmol) and purified by column chromatography (1% EtOAc/hexane) to give an inseparable mixture of starting material and product (6:1) as a colourless oil (97 mg, 48%). R_f = 0.44 (20% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (8H, m, Ar**H**), 7.18-7.17 (2H, m, Ar**H**), 5.02 (2H, s, C**H**$_2$Ph), 4.07 (1H, m, C**H**CH_2), 3.18 (1H, dd, J = 16.1, 4.4 Hz, CHC**H**$_2$), 2.99 (1H, dd, J = 16.1, 10.3 Hz, CHC**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.8 (C), 135.3 (C), 133.3 (C, t, J = 5.5 Hz), 129.4 (2 x CH), 128.6 (2 x CH), 128.53 (CH), 128.51 (2 x CH), 128.3 (CH), 128.1 (2 x CH), 118.4 (C, qt, J = 255.7, 34.7 Hz), 116.6 (C, tt, J = 235.4, 29.5 Hz), 109.4 (C, tq, J = 265.9, 38.2 Hz), 66.8 (CH_2), 44.1 (CH, t, J = 21.0 Hz), 34.3 (CH_2, t, J = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.6 (3F, dd, J = 12.3, 9.9 Hz), –112.7 (1F, ddqd, J = 277.6, 14.7, 12.3, 4.1 Hz), –116.7 (1F, ddqd, J = 277.6, 14.7, 9.9, 9.3 Hz), –122.8 (1F, ddd, J = 290.2, 14.7, 9.3 Hz), –125.0 (1F, ddd, J = 290.2, 14.7, 4.1 Hz). GC-MS (EI) *m/z* 408 (2%), 388 (2%), 273 (8%), 91 (100%).



Methyl 4,4,4-trifluoro-3-(4-fluorophenyl)butanoate (149h).

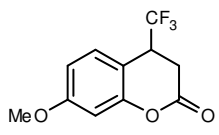
The title compound was prepared according to General Procedure D from **145h** (124 mg, 0.50 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a colourless oil (87 mg, 70%). R_f = 0.34 (20% EtOAc/hexane); IR (film) 1743 (C=O), 1514, 1439, 1308, 1258, 1227, 1155, 1109, 966, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (2H, dd, *J* = 8.5, 5.3 Hz, Ar**H**), 7.09-7.04 (2H, m, Ar**H**), 3.90 (1H, dqd, *J* = 10.0, 9.3, 4.8 Hz, C**H**CF_3), 3.62 (3H, s, OC**H**$_3$), 3.04 (1H, dd, *J* = 16.4, 4.8 Hz, C**H**$_2CO_2Me$), 2.88 (1H, dd, *J* = 16.4, 10.0 Hz, C**H**$_2CO_2Me$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.3 (C), 162.7 (C, d, *J* = 247.7 Hz), 130.6 (2 x CH, d, *J* = 8.3 Hz), 129.5 (C, dq, *J* = 6.0, 2.5 Hz), 126.2 (C, q, *J* = 279.7 Hz), 115.8 (2 x CH, d, *J* = 21.6 Hz), 52.1 (CH_3), 45.4 (CH, q, *J* = 28.0 Hz), 34.3 (CH_2, q, *J* = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.7 (3F, s), –113.4 (1F, s); HRMS (EI) Exact mass calcd for $C_{11}H_{10}F_4O_2$ [M^+]: 250.06114, found: 250.06184.



Methyl 4,4,4-trifluoro-3-(4-methylphenyl)butanoate (149j).

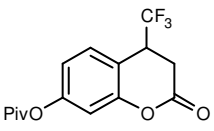
The title compound was prepared according to General Procedure D from **145j** (122 mg, 0.50 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a colourless oil (94 mg, 76%). R_f = 0.53 (20% EtOAc/hexane); IR (film) 1744 (C=O), 1439, 1302, 1258, 1217, 1153, 1105, 964, 912, 806 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.18 (2H, d, *J* = 8.0 Hz, Ar**H**), 3.90 (1H, dqd, *J* = 9.8, 9.4, 5.1 Hz, C**H**CF_3), 3.62 (3H, s, OC**H**$_3$), 3.03 (1H, dd, *J* = 16.3, 5.1 Hz, C**H**$_2CO_2Me$), 2.90 (1H, dd, *J* = 16.3, 9.8 Hz, C**H**$_2CO_2Me$), 2.35 (3H, s, ArC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.6 (C), 138.3 (C), 130.6 (C, q, *J* = 1.8 Hz), 129.4 (2 x CH), 128.7 (2 x CH), 126.4 (C, q, *J* = 279.6 Hz), 52.0 (CH_3), 45.7 (CH, q, *J* = 27.7 Hz), 34.2 (CH_2, q, *J* = 2.3 Hz), 21.1 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{13}F_3O_2$ [M^+]: 246.08622, found: 246.08641.

7-Methoxy-4-(trifluoromethyl)-3,4-dihydro-2H-1-benzopyran-2-one (149k)



The title compound was prepared according to General Procedure D from **145k** (122 mg, 0.50 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a white solid (95 mg, 77%). R_f = 0.24 (20% EtOAc/hexane); m.p. 78-

80 °C; IR (solid) 1746 (C=O), 1516, 1439, 1306, 1260, 1227, 1157, 1111, 966, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.75 (1H, dd, *J* = 8.5, 2.6 Hz, Ar**H**), 6.66 (1H, d, *J* = 2.6 Hz, Ar**H**), 3.82 (3H, s, OC**H**$_3$), 3.68-3.61 (1H, m, C**H**CF_3), 3.14 (1H, dd, *J* = 17.0, 1.9 Hz, C**H**$_2$C=O), 2.95 (1H, dd, *J* = 17.0, 7.4 Hz, C**H**$_2$C=O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.9 (C), 161.5 (C), 153.2 (C), 130.6 (CH), 125.6 (C, q, *J* = 280.5 Hz), 111.2 (CH), 106.6 (C, q, *J* = 1.8 Hz), 102.8 (CH), 55.6 (CH_3), 39.6 (CH, q, *J* = 29.7 Hz), 28.7 (CH_2, q, *J* = 2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.1 (3F, s); HRMS (EI) Exact mass calcd for $C_{11}H_9O_3F_3$ [M^+]: 246.0498, found: 246.0499.



2-oxo-4-(trifluoromethyl)-3,4-dihydro-2H-1-benzopyran-7-yl 2,2-dimethylpropanoate (149l)

The title compound was prepared according to General Procedure D from **145l** (157 mg, 0.50 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a white solid (80 mg, 51%). R_f = 0.29 (20% EtOAc/hexane); m.p. 94-98 °C; IR (solid) 1746 (C=O), 1516, 1439, 1306, 1261, 1225, 1159, 1113, 966, 557 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.93 (1H, dd, *J* = 8.4, 2.3 Hz, Ar**H**), 6.88 (1H, d, *J* = 2.3 Hz, Ar**H**), 3.75-3.67 (1H, m, C**H**CF_3), 3.15 (1H, dd, *J* = 17.0, 1.9 Hz, C**H**$_2$C=O), 2.97 (1H, dd, *J* = 17.0, 7.4 Hz, C**H**$_2$C=O), 1.36 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.5 (C), 164.2 (C), 152.70 (C), 152.70 (C), 130.6 (CH), 125.4 (C, q, *J* = 280.5 Hz), 118.2 (CH), 112.2 (C, q, *J* = 1.6 Hz), 111.3 (CH), 39.8 (C, q, *J* = 29.8 Hz), 39.1 (C), 28.4 (CH_2, q, *J* = 2.5 Hz), 27.0 (3 x CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –72.7 (3F, s); HRMS (EI) Exact mass calcd for $C_{15}H_{15}O_4F_3$ [M^+]: 316.09170, found: 316.09123.

5. Enantioselective Metal-Catalysed Arylations of *β*-Fluoroalkyl-*α*,*β*-Unsaturated Carbonyl Compounds

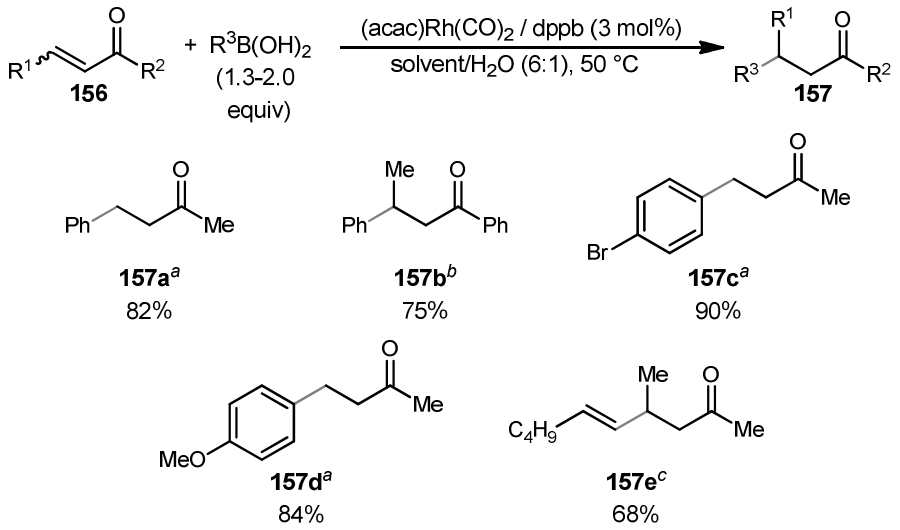
Asymmetric carbon–carbon bond-forming reactions are of great utility in organic synthesis. One of the most popular methods is the metal-catalysed conjugate addition. As part of our exploration of the reactivity of *β*-fluoroalkyl-*α*,*β*-unsaturated carbonyl compounds, we wished to develop the introduction of further functionality into these substrates enantioselectively though the formation of a carbon–carbon bond.

Organoboron species (and boronic acids in particular) are excellent nucleophiles for such reactions.[113] This effectiveness is due to their good stability towards air and moisture relative to other organometallic reagents, their lack of reactivity in the absence of catalyst (which prevents a decrease in enantiomeric excess due to uncatalysed background reactions), their wide availability and generally low toxicity. One class of reaction which has been explored over the past fifteen years is the rhodium-catalysed arylation of enones.

5.1 Introduction

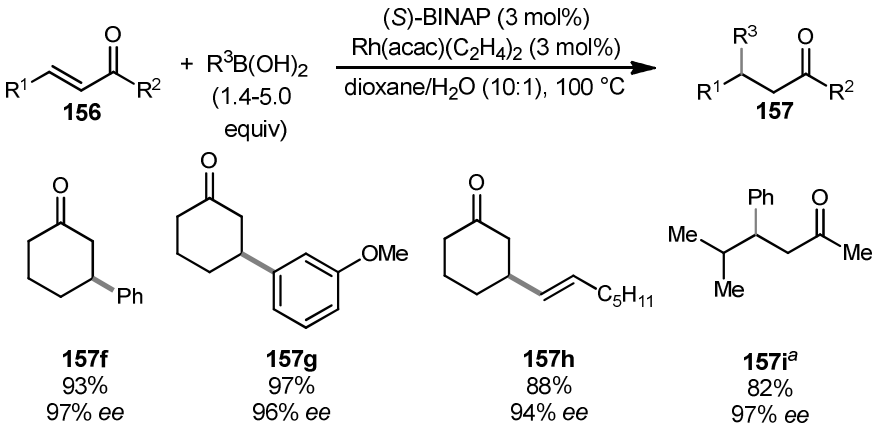
5.1.1 Rhodium-Catalysed 1,4-Arylations of *α*,*β*-Unsaturated Carbonyl Compounds

The first report of the 1,4-addition of aryl and alkenyl boronic acids to *α*,*β*-unsaturated ketones under rhodium catalysis came from the group of Miyaura in 1997 (**Scheme 5.1**).[114] Screening conducted on methyl vinyl ketone revealed that a number of phosphine ligands worked well in the reaction, but dppb was eventually selected for further experimentation. There were also a number of rhodium catalysts and solvents that could be employed, but the addition of water to the mixture was found to be essential for high yields. A range of substrates and boronic acids were shown to undergo reaction under the optimised conditions to give good yields of the isolated ketone products.



Scheme 5.1 [a]DMF [b]cyclohexane [c]MeOH

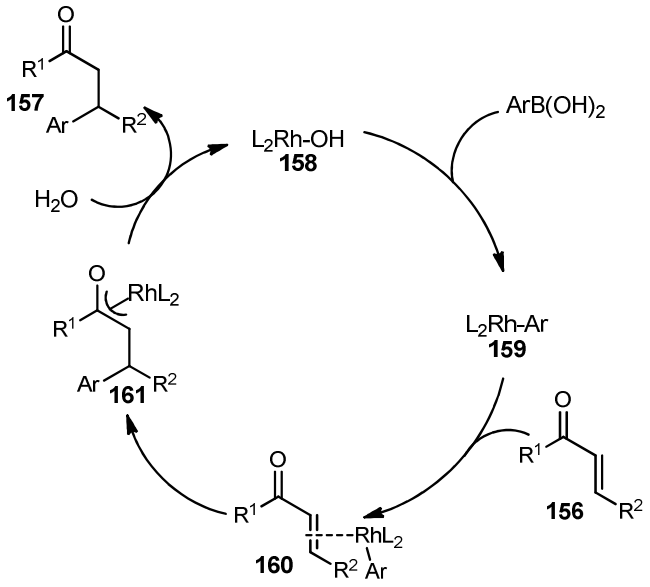
The first enantioselective example of the rhodium-catalysed 1,4-arylation of enones was published by Hayashi and Miyaura in 1998.[115] BINAP was the chiral ligand of choice for this reaction and there were also changes to the rhodium catalyst ($Rh(acac)(C_2H_4)_2$) and solvent (dioxane/water 10:1) used. *Ee*s for a range of substrates and boronic acids were all above 90% and the observed yields were also generally very good (**Scheme 5.2**).



Scheme 5.2 [a]Absolute geometry not determined

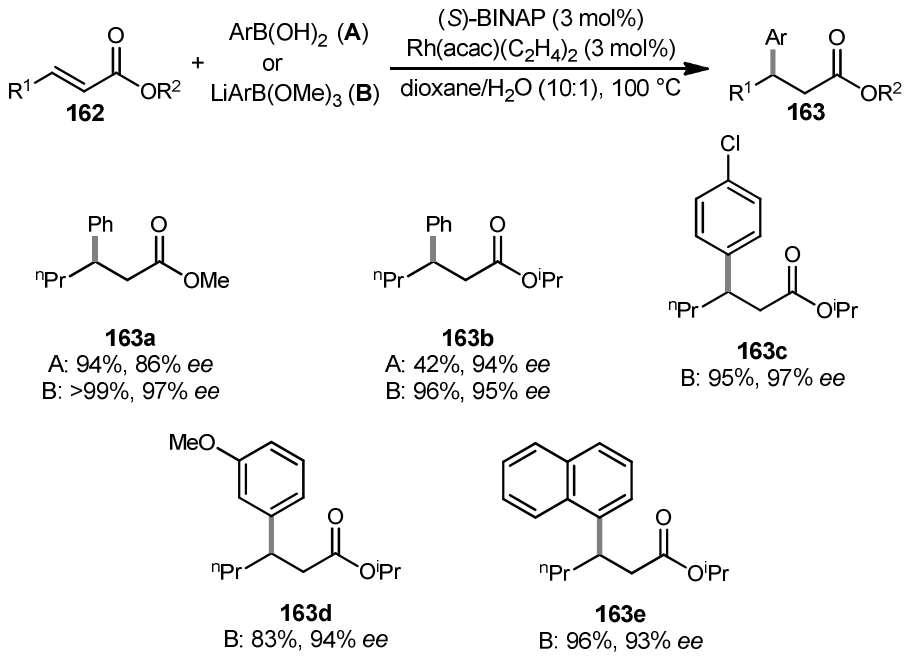
An initial proposed mechanism was given in this communication and further details were disclosed in a full paper from 2002.[116] A basic outline is given in **Scheme 5.3**. The cycle begins with the transmetallation of the aryl group from the boron centre to rhodium to give a rhodium-aryl species (**159**). Co-ordination of the rhodium species to the alkene of the substrate is followed by insertion of the enone into the rhodium-aryl bond to give a rhodium

enolate (**161**). The hydrolysis of this enolate is then required to release a molecule of product (**157**) and regenerate the active catalyst. All of the intermediates were observed in NMR experiments. The detailed mechanistic study also led to the discovery of a more active catalyst complex. It was discovered that a temperature of above 60 °C was required for transmetallation to Rh(acac)(BINAP), whereas transmetallation to [$Rh(OH)_2$(BINAP)] occurs rapidly at 25 °C. The [$Rh(OH)_2$(BINAP)] complex can be generated *in situ* from $[RhCl(BINAP)]_2$ if KOH is added.



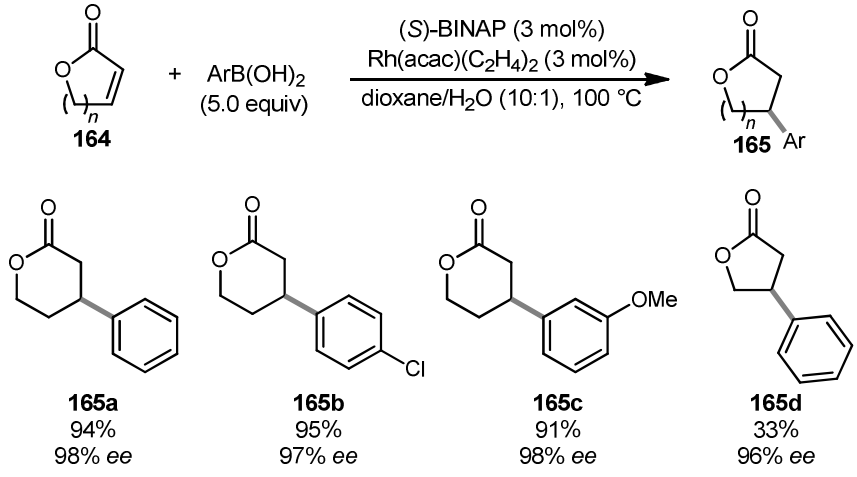
Scheme 5.3

The first report of the extension of rhodium-catalysed arylation methodology to *α,β*-unsaturated esters was described by Hayashi in 1999.[117] The application of both boronic acids and *in-situ*-generated lithium borates (which were originally reported by the same authors earlier in the same year[118]) was described, with the latter giving more general results (**Scheme 5.4**). Both yields and enantiomeric excesses are excellent.



Scheme 5.4

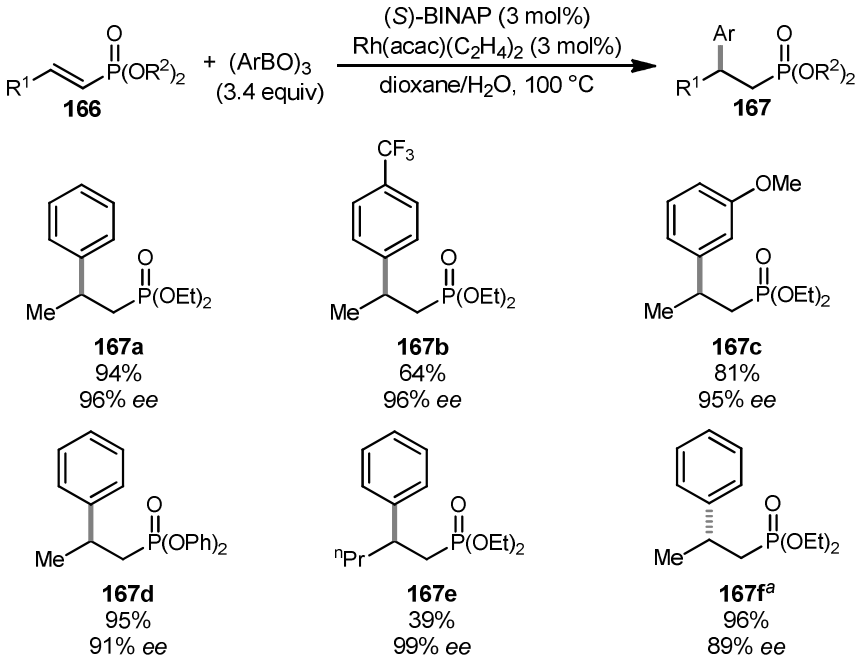
Unsaturated lactones were also found to be arylated smoothly using rhodium catalysis. In this case, arylboronic acids were found to be the best aryl source. Again, yields and *ee*s were generally excellent, although the isolated yield for a five-membered ring substrate was poor (**Scheme 5.5**). In a slightly later publication by Miyaura, almost identical conditions were arrived at after extensive screening.[119]



Scheme 5.5

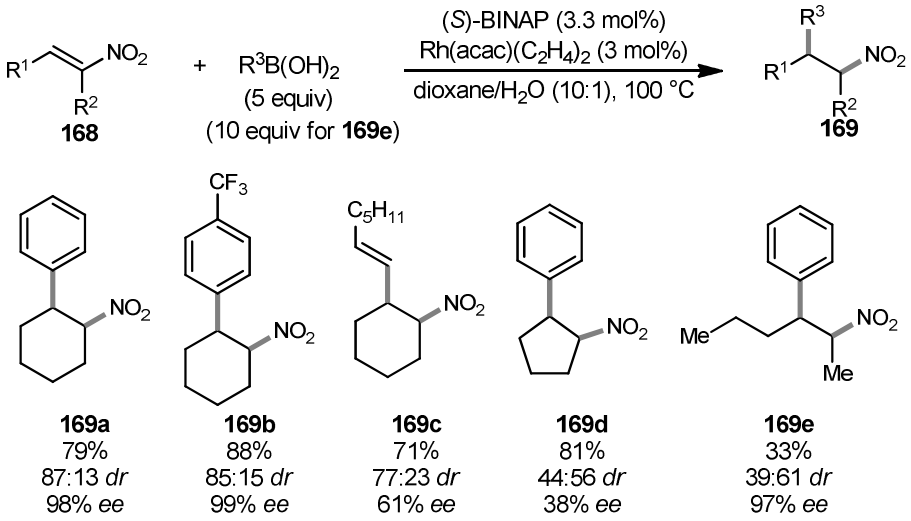
The next substrates for which rhodium-catalysed conjugate arylations were found to be successful were alkenylphosphonates.[120] Reaction yields were found to be disappointingly

low when boronic acids were employed. However, the application of triarylcyclotriboroxines gave the desired products in generally excellent yields and *ee*s (**Scheme 5.6**). Employing a substrate with the opposite double bond geometry gave the opposite enantiomer as product (**167a** and **167f**). The slow isomerisation of the *Z* starting material into the *E* was observed under the reaction conditions, giving decreased *ee*s with prolonged reaction times.



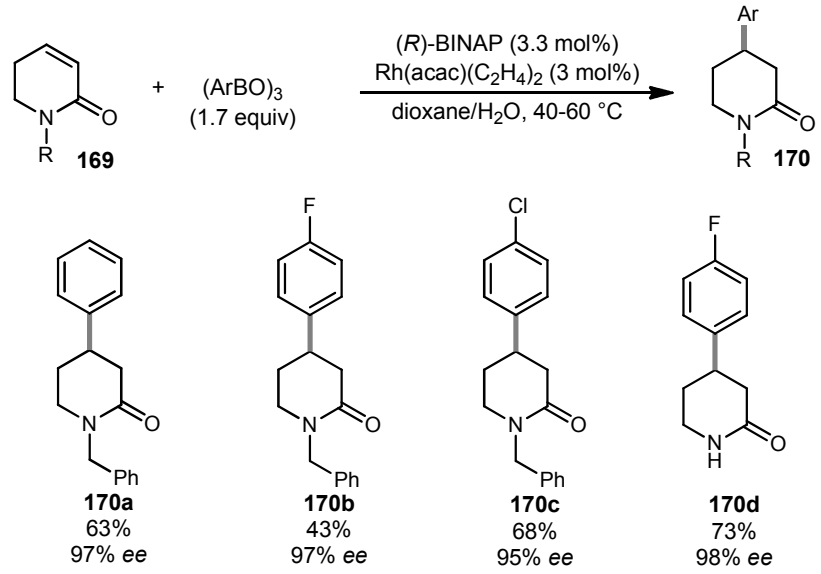
Scheme 5.6 [a]Substrate was (*Z*)-isomer

The asymmetric arylation of nitroalkenes has also been reported.[121] The conditions employed were the same as those described previously for unsaturated ketones, esters and phosphonates. Yields and enantiomeric excesses were excellent for the arylation of 6-membered ring substrates, but *ee*s were decreased for the alkenylation of these substrates and the arylation of 5-membered rings (**Scheme 5.7**). An acyclic substrate also underwent reaction (**169e**), although the yield was significantly lower even when 10 equivalents of boronic acid was employed.



Scheme 5.7

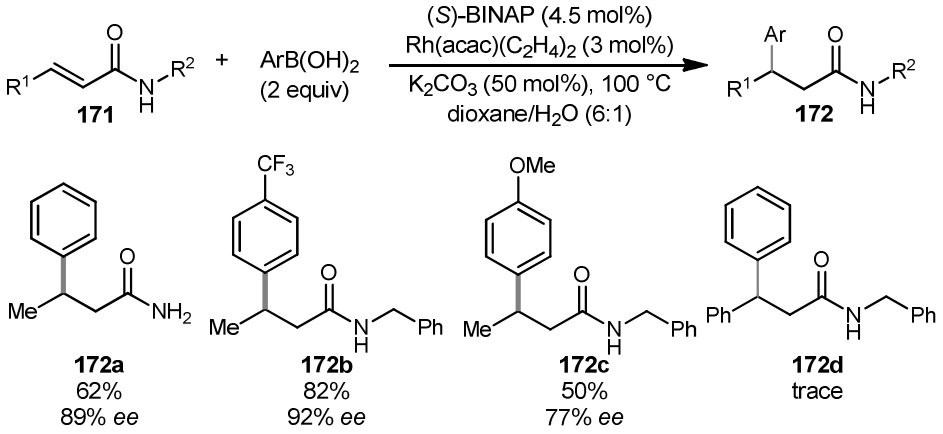
The rhodium-catalysed arylation of cyclic α,β-unsaturated amides was reported in 2001.[122] The examples given were limited to the reaction of one substrate with three arylboroxines: phenyl and the electron-deficient *p*-F-phenyl and *p*-Cl-phenyl (**Scheme 5.8**). For the *p*-F-phenyl example, the isolated yield of product was found to be significantly higher for the substrate with a free N-H than for that with a benzyl protecting group.



Scheme 5.8 Absolute geometry not determined

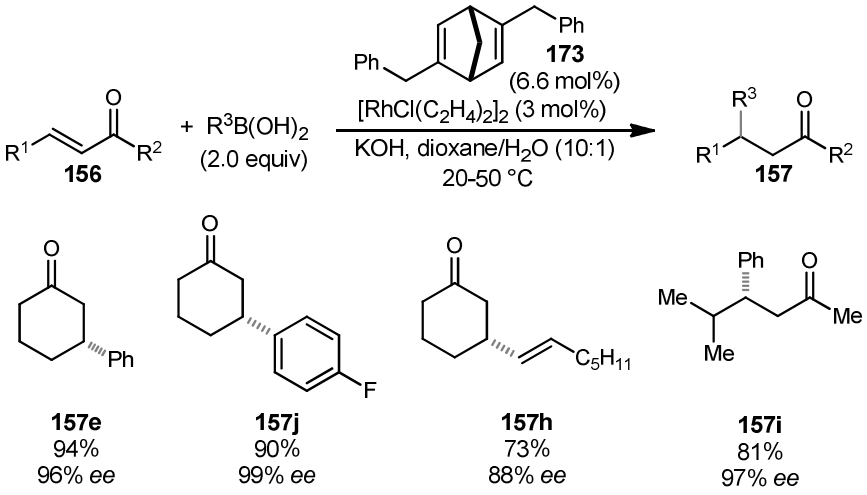
Acyclic unsaturated amides were reported as successful substrates in rhodium-catalysed arylations later the same year.[123] Initially, the reaction gave poor conversions, which resulted in low yields. However, it was found that the addition of base, which allows the formation of

RhOH species *in situ*, led to increased conversions due to the accelerated rate of transmetallation of the aryl group to the rhodium centre (*vide supra*). The reaction worked well for a range of substituents on the nitrogen atom (although no reaction is observed when dialkyl amides were tested) and boronic acids (**Scheme 5.9**). The *β*-substituent had a greater effect on the reaction with only a trace of product being obtained with a phenyl substituent (**172d**).



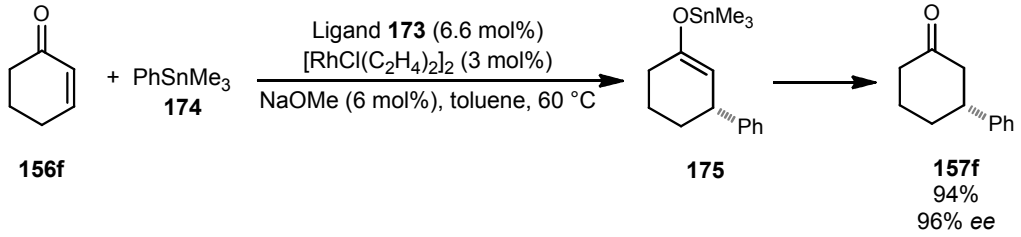
Scheme 5.9

So far, the only chiral ligand that we have seen employed in these rhodium-catalysed arylations is BINAP. However, in 2003, Hayashi reported the first use of chiral dienes as ligands.[124] The use of the resulting new catalyst complex allowed arylations to occur at lower temperatures than in previous reports, with cyclohexenone undergoing reaction with phenyl boronic acid at 20 °C. A range of cyclic and acyclic enones were reacted with aryl and alkenyl boronic acids to give the expected products in excellent yields and enantiomeric excesses (**Scheme 5.10**).



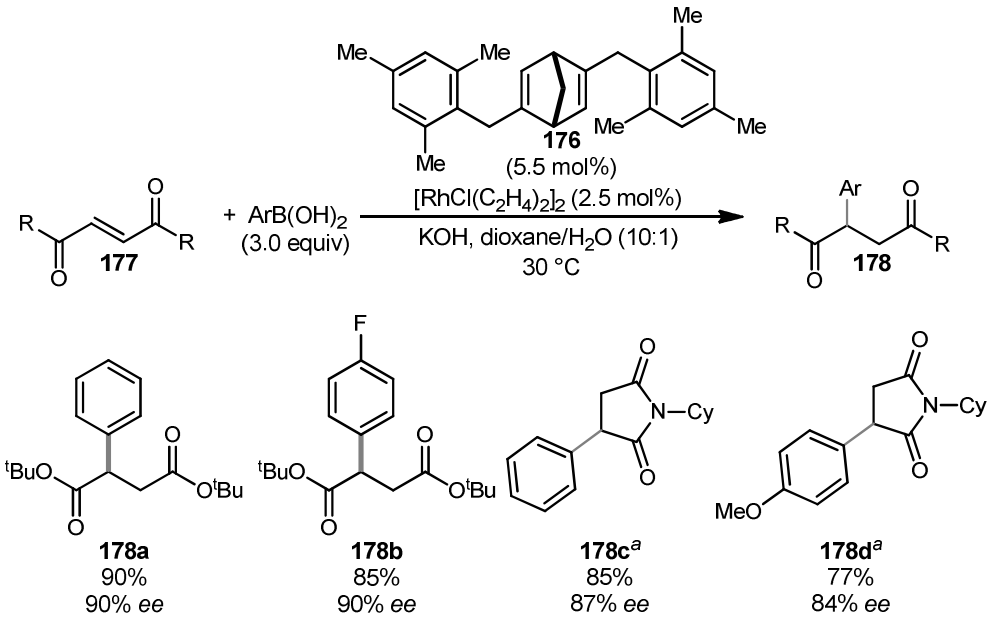
Scheme 5.10

In this publication, the use of the less reactive stannanes as an aryl source was shown to be successful with diene ligands (**Equation 5.1**). Previously, attempts employing (*S*)-BINAP had given yields of lower than 10%.



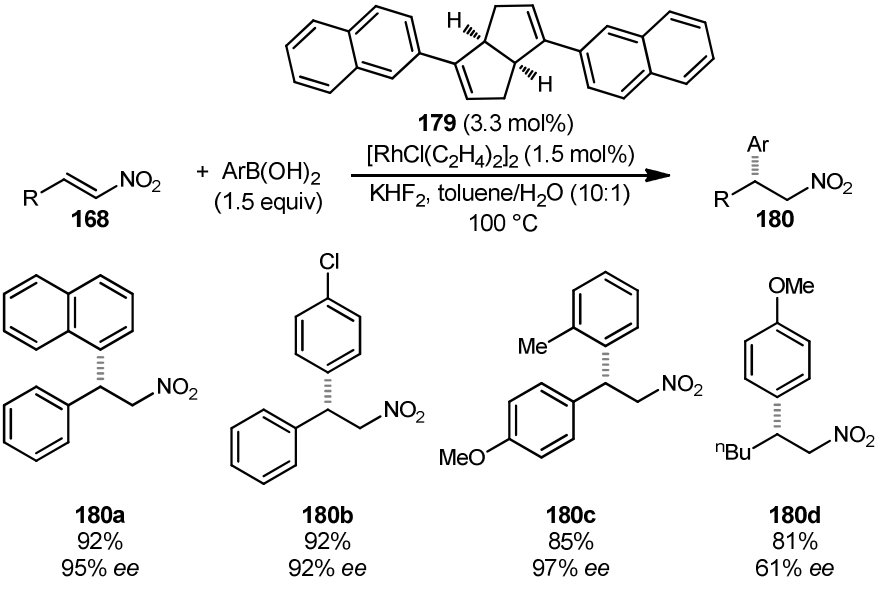
Equation 5.1

Another reported application of diene ligands is in the arylation of fumaric and maleic compounds; a substrate class which had previously not been successful in the rhodium-catalysed process.[125] Chiral norbornadiene ligand **176** was found to be the most efficient and a range of 2-substituted-1,4-dicarbonyl compounds were synthesised in excellent yields and enantiomeric excesses in the range of 82-92 % (**Scheme 5.11**).



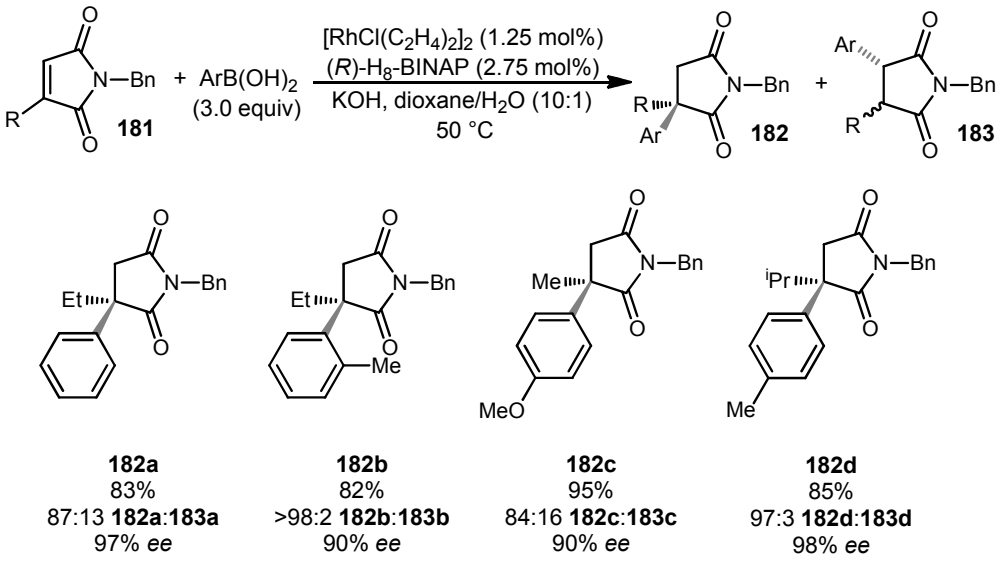
Scheme 5.11 [a]Absolute geometry not determined

Diene ligands have also been used by the group of Zu and Lin in their expansion of the substrate scope for nitroalkene arylations to include those without an α-substituent (**Scheme 5.12**).[126] Enantiomeric excesses were excellent (95-97% *ee*) when bulky arylboronic acids (1-naphthyl and 2-tolyl) were employed and were generally good for all substrates with an aryl substituent (82-97% *ee*). However, a drop in enantiomeric excess values was observed for alkyl substituted nitroalkenes (e.g. **180d**).



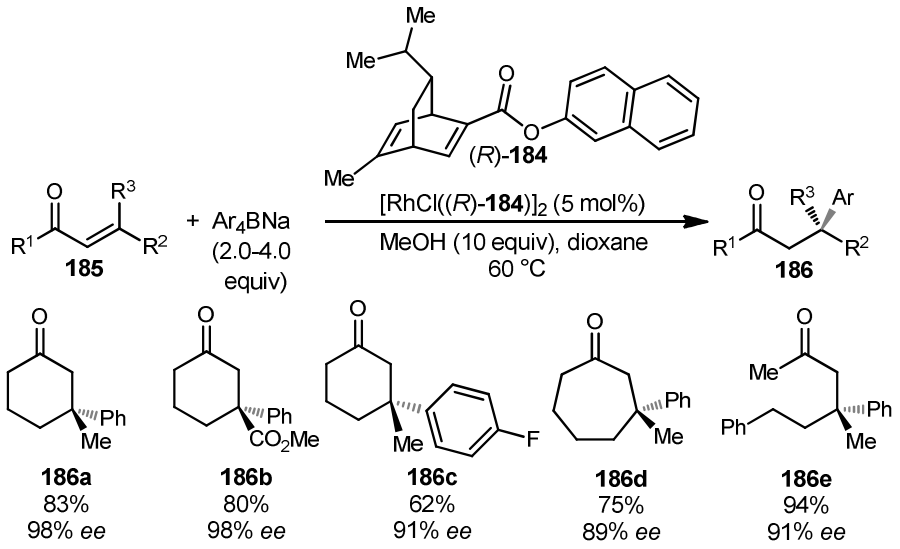
Scheme 5.12

The first example of the rhodium-catalysed conjugate arylation to form quaternary stereocentres was reported by Hayashi in 2006.[127] 3-Substituted maleimides underwent reaction with (*R*)-H_8-BINAP as ligand to give 3,3-disubstituted succinimides with excellent regio- and enantioselectivity (**Scheme 5.13**).



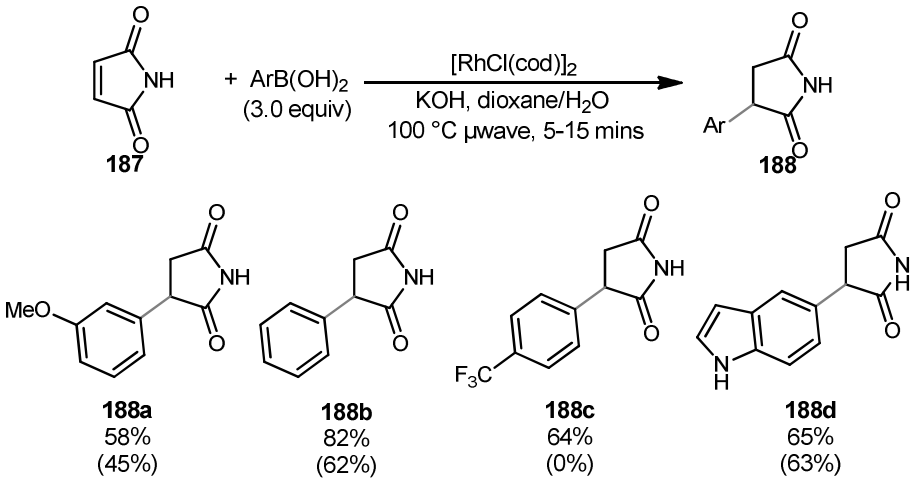
Scheme 5.13

Rhodium-catalysed arylations generating quaternary stereocentres were extended to cyclic and acyclic enone substrates by the same group in 2009.[128] In this publication, sodium tetraarylborate salts were used in place of boronic acids as the aryl source. It is believed that the advantage of these air stable borate salts is a result of the release of triarylborane, which acts as a Lewis acid to assist the insertion of substrate into the rhodium-aryl bond. Yields and *ee*s were excellent for a range of substrates and aryl groups (**Scheme 5.14**).



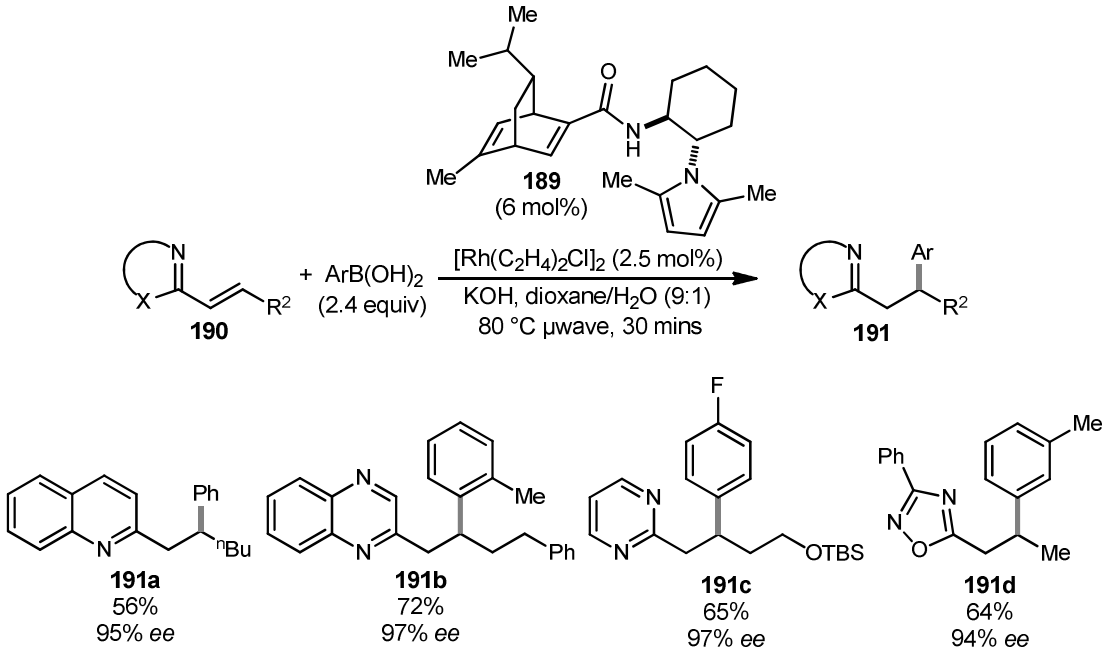
Scheme 5.14

In 2007, Iyer and co-workers described the results of a study using microwave irradiation in the racemic rhodium-catalysed arylation of maleimides using boronic acids.[129] Not only were reaction times found to be shorter, but the scope was found to be broader under their conditions. Protection of the maleimide nitrogen was no longer required and electron deficient boronic acids, which failed to react under conventional heating, gave good yields (**Scheme 5.15**). However, *ortho*-substituted boronic acids were found not to react under either set of conditions.

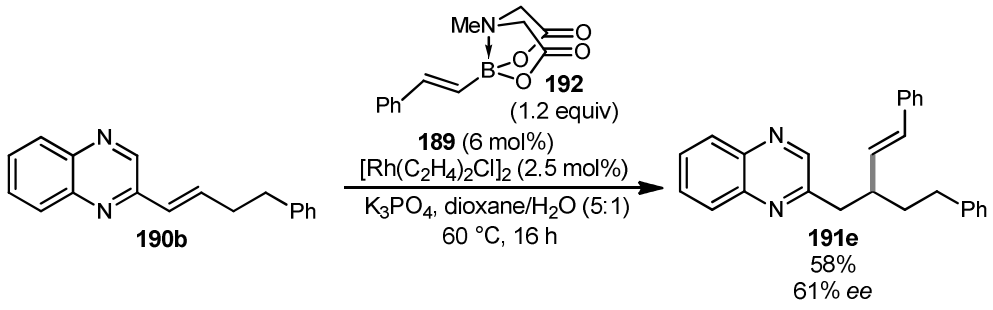


Scheme 5.15 Yields in parenthesis indicate those obtained under conventional heating at 50 °C for 6 hours. Absolute geometries were not determined.

The first contribution from the Lam group to rhodium-catalysed arylation chemistry was published in 2010 and demonstrates the reaction of alkenylheteroarenes.[130] A range of heterocyclic substrates were shown to react with a number of different boronic acids in excellent yields and enantiomeric excesses (**Scheme 5.16**) employing a novel chiral diene ligand **189**. Alkenyl boronic acids were shown to be more troublesome giving only small quantities of the desired product under various conditions. Protodeboration was the major outcome. MIDA-boronate **192** which releases the appropriate boronic acid gradually under basic conditions was found to give superior results, although the enantiomeric excess was still modest at 61% (**Equation 5.2**).



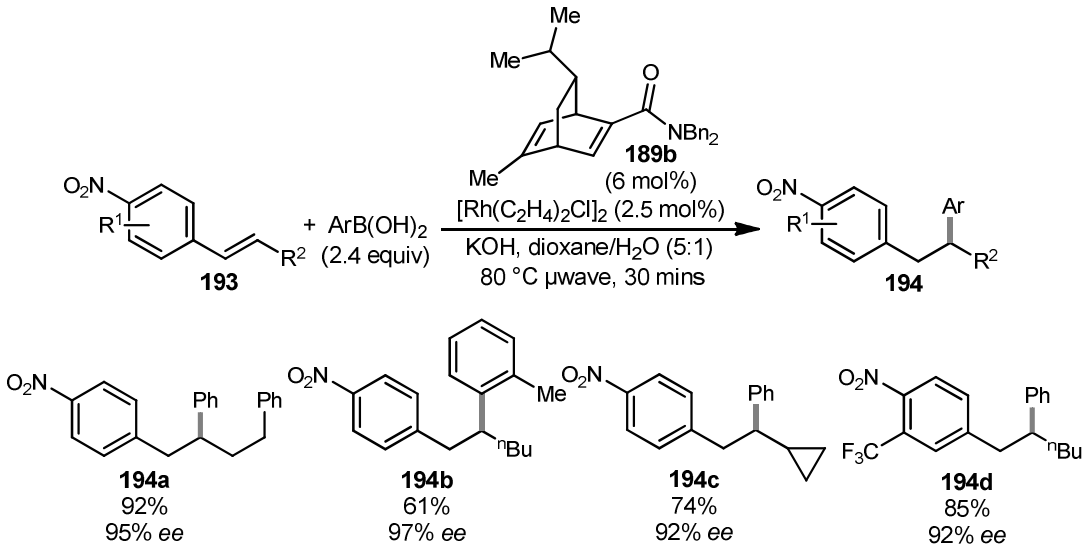
Scheme 5.16



Equation 5.2

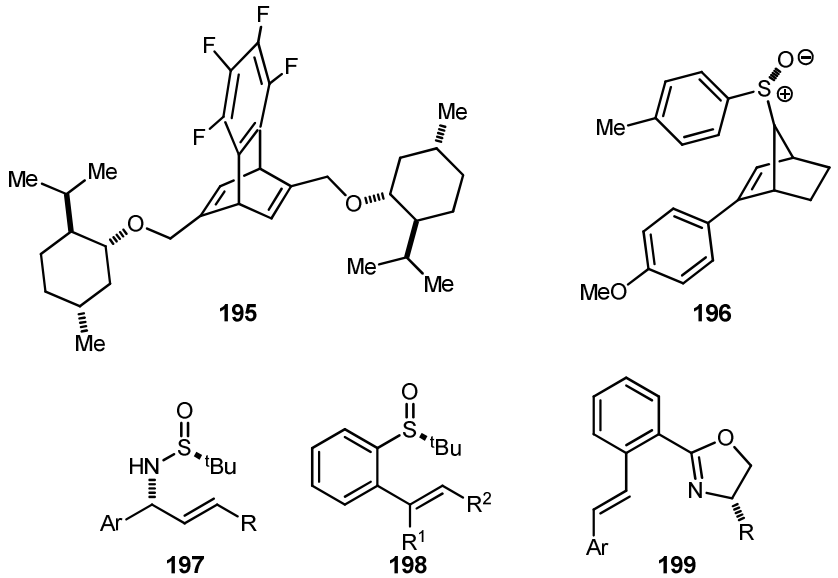
A further report has also described the reaction of alkenyl nitroarenes in a similar manner.[131] The diene ligand employed was changed to dibenzyl amide **189b** and additional water was

added, but otherwise the optimised conditions matched those required for the reaction of alkenylheteroarenes. Again, yields and *ee*s were found to be very high for a number of substrates and boronic acids (**Scheme 5.17**).



Scheme 5.17

Other reports from the past three years have often focused on the synthesis of new ligand classes, which have been shown to be successful in the arylation of cyclic enones. Examples include tetrafluorobenzobarrelenes (**195**)[132], several different sulfoxide-alkene hybrids (**196**-**198**)[133] and olefin-oxazoline (**199**)[134] (**Scheme 5.18**).

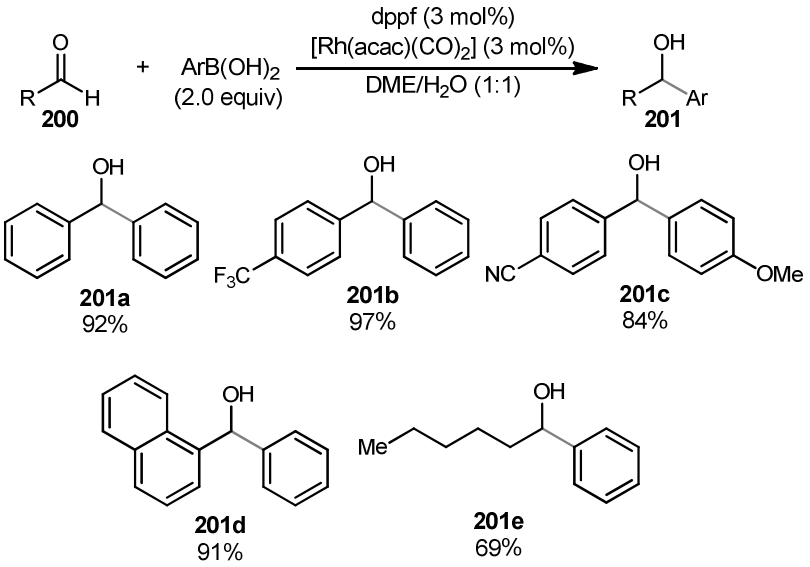


Scheme 5.18

However, it is not just enantioselective conjugate additions of arylboronic acids that can be catalysed by rhodium. 1,2-Arylations have also been reported.

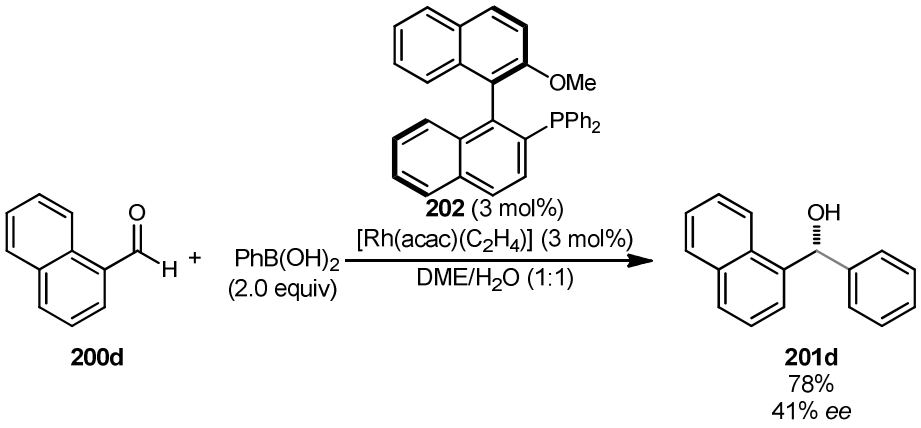
5.1.2 Rhodium-Catalysed 1,2-Arylations of Carbonyl Compounds

The seminal report of rhodium-catalysed 1,2-arylation using boronic acids came from Miyaura in 1998.[135] The optimised conditions involve dppf as ligand and a mixture of DME and water as solvent. The reaction of a range of aldehydes and boronic acids was found to proceed smoothly under these conditions (**Scheme 5.19**). Problematic reactants included the electron-poor 4-nitrobenzaldehyde and the use of 4-acetylphenyl boronic acid, which both returned the aldehyde starting material unchanged.



Scheme 5.19

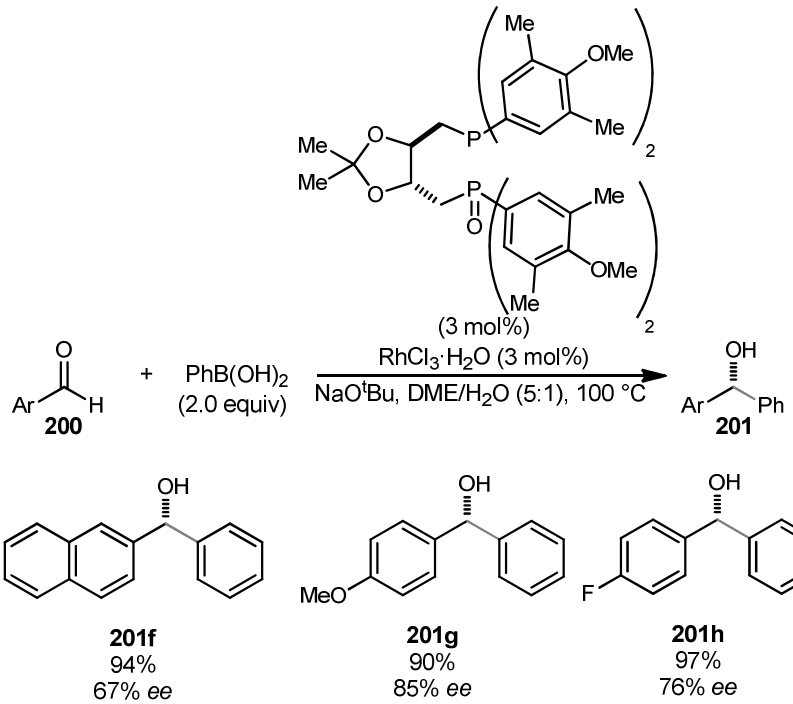
This publication also describes the earliest attempt at an enantioselective version. Employing (*S*)-MeO-MOP (**202**) as ligand, 1-naphthaldehyde was arylated with phenyl boronic acid to give the expected diarylmethanol product in 78% yield and 41% *ee* (**Equation 5.3**).



Equation 5.3

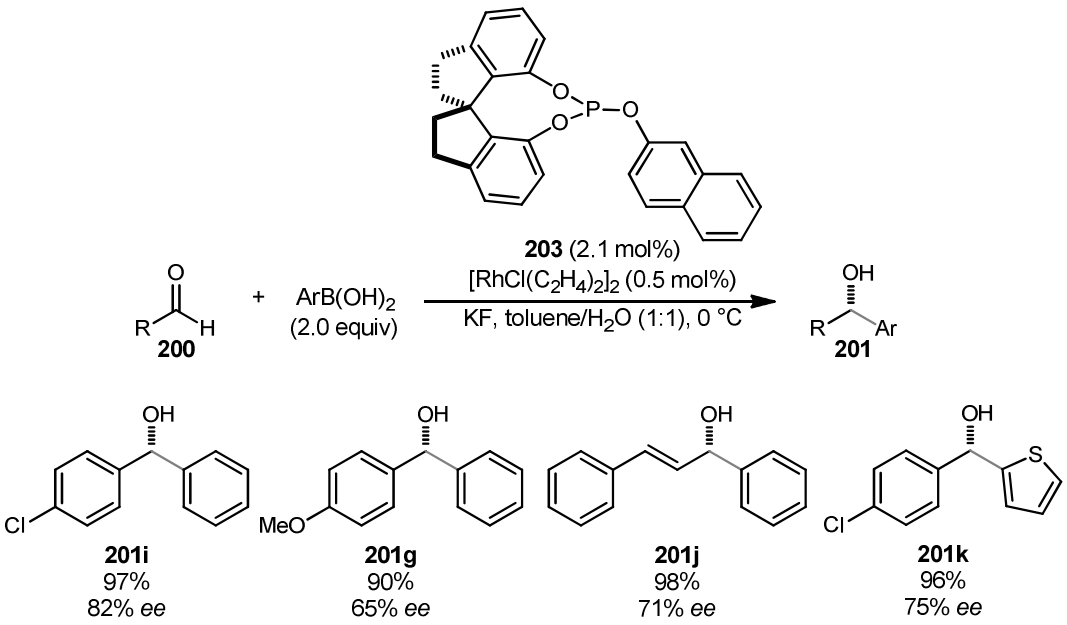
Following this publication, there have been many attempts to optimise the *ee*s for the arylation of aldehydes, most of which have met with limited success. The first of these came from the group of Bolm in 2005 and described the use of imidazolium salts as ligands.[136] Seven different salts were screened but the best *ee* obtained for the reaction of 4-chlorobenzaldehyde with phenyl boronic acid was only 29%.

There were several further reports in 2006. In one, a number of chiral bisphosphine ligands were screened and ^{i}Pr-DuPhos was discovered to give the best enantioselectivity.[137] For the eight examples described, the *ee*s ranged from 36 to 66%. Higher enantioselectivity values were obtained by the same authors with the use of a hemilabile ligand (**Scheme 5.20**).[138]



Scheme 5.20

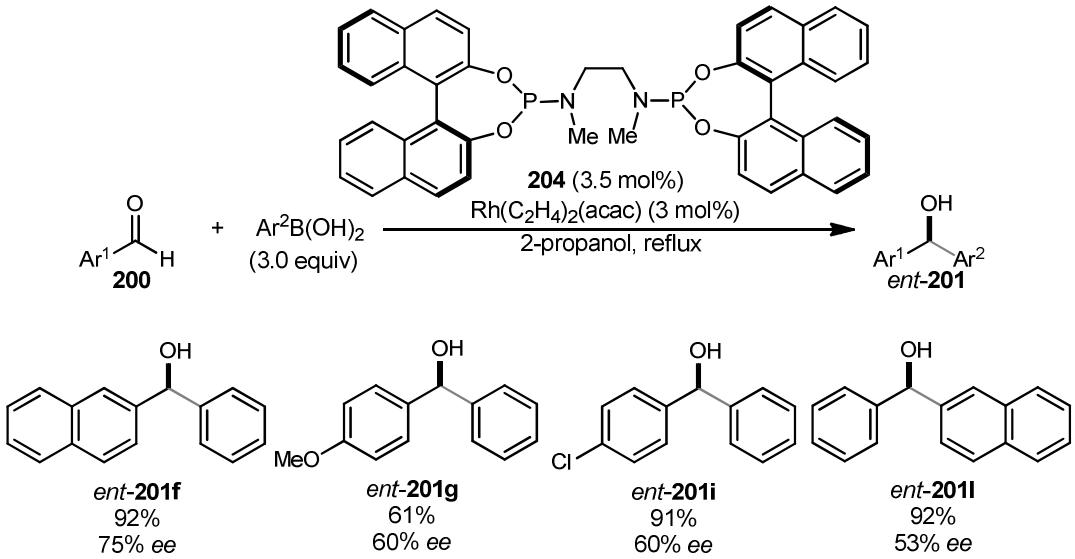
Excellent yields and good *ee* values were obtained when chiral *spiro* monophosphite ligand **203** was used (**Scheme 5.21**).[139]



Scheme 5.21

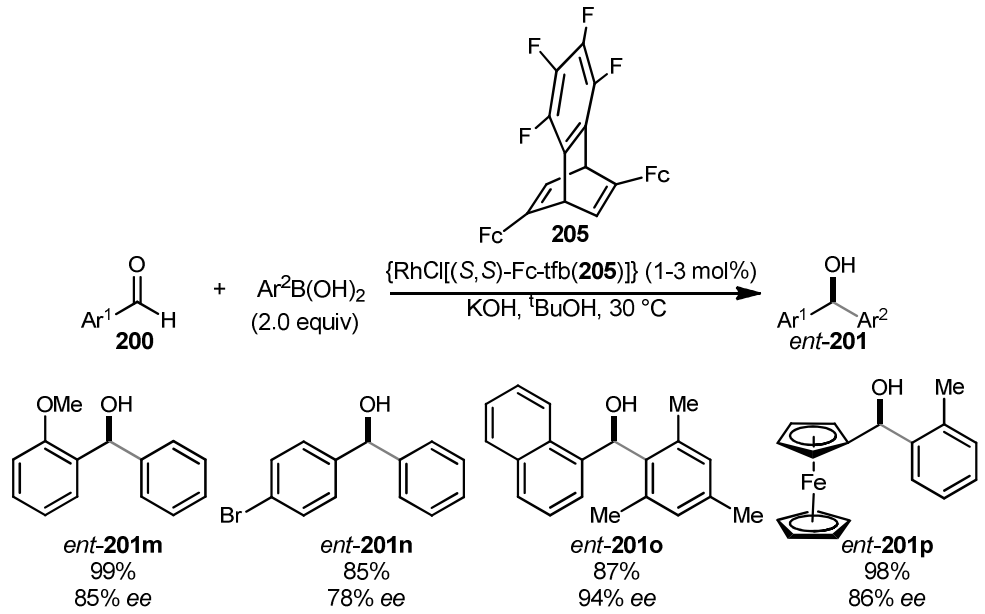
A report from Feringa, Minnaard and co-workers on the use of bidentate phosphoramidite ligands displayed *ee*s of up to 75% (**Scheme 5.22**).[140] The authors also expanded on the effect

of the ligand in the arylation of aldehydes with an extensive phosphoramidite and phosphite library screening study.[141] No increases in enantioselectivity were reported, but it was discovered that different substrate classes gave their best results with different ligands.



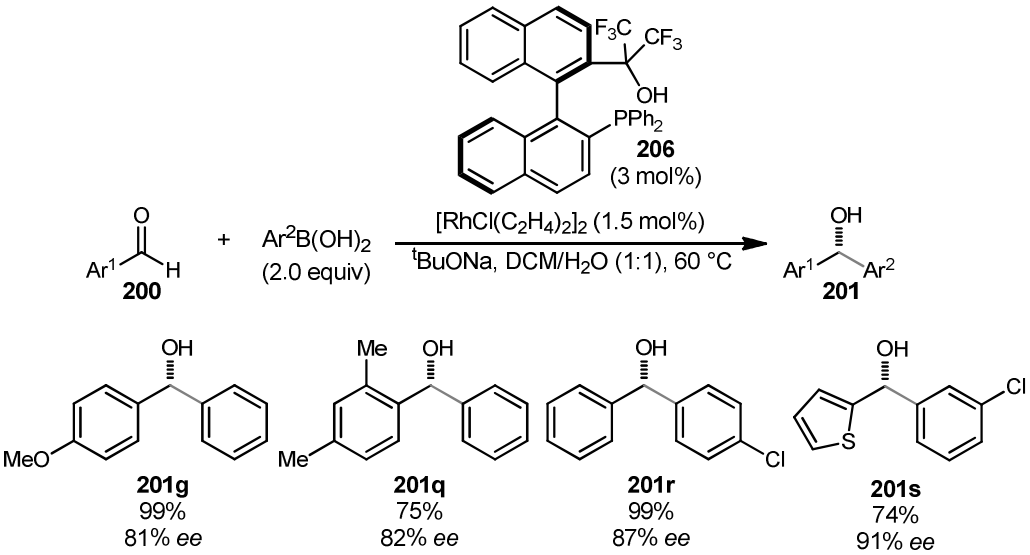
Scheme 5.22

As the use of diene ligands has seen such success in enantioselective rhodium-catalysed conjugate arylations, it is not surprising that their use in direct arylations has been reported.[142] Screening was carried out on the reaction of phenylboronic acid with *p*-trifluoromethylbenzaldehyde using a bicycloheptadiene ligand. Unfortunately, the highest *ee* obtained whilst retaining a high yield was 42%. More success has been achieved with tetrafluorobenzobarrelene ligands, for which yields were excellent and the enantiomeric excesses were much higher (**Scheme 5.23**).[143] The authors attribute the success of this ligand class to their good coordination ability toward transition metals, their small bite angle and their electron-deficient character. Additionally, the synthesis of these ligands is straightforward, requiring a simple [4 + 2] cycloaddition.



Scheme 5.23

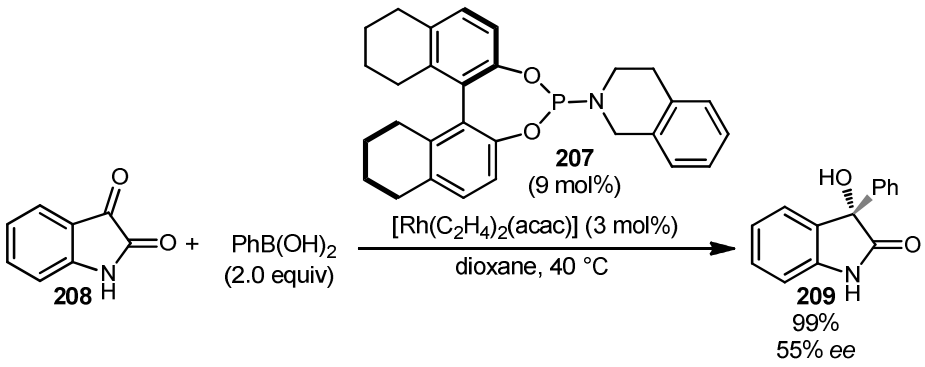
Another publication in which good enantiomeric excesses are obtained describes the use of axially chiral fluoroalcohol-substituted phosphine ligands **206**.[144] The paper contains 13 examples of the arylation of aldehydes all with *ee*s higher than 80% (**Scheme 5.24**).



Scheme 5.24

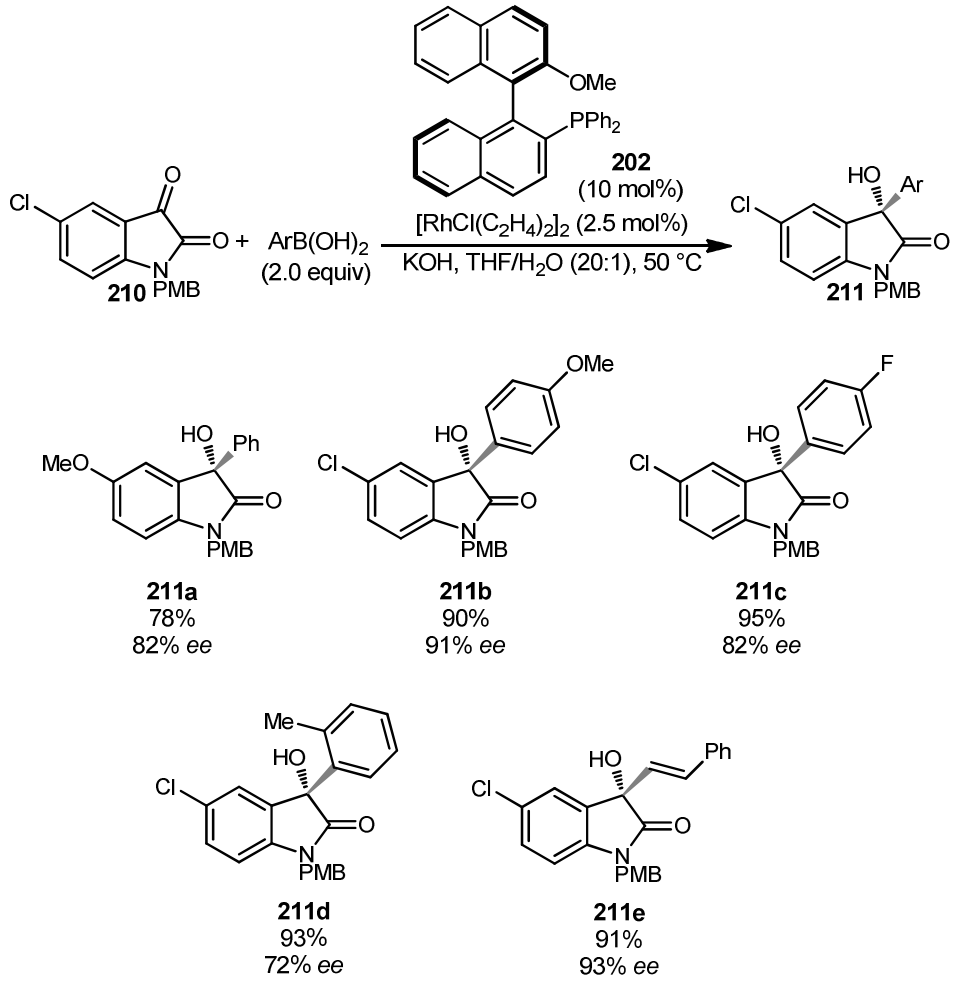
There are fewer examples of the enantioselective rhodium-catalysed arylation of ketones and, until very recently, only particularly electrophilic ketones had been successfully reacted. One example of a successful substrate class is isatins. Two reports of their arylation appeared in a

short space of time. The first describes a racemic reaction with one asymmetric example employing a phosphoramidite ligand and giving an *ee* of 55% (**Equation 5.4**).[145]



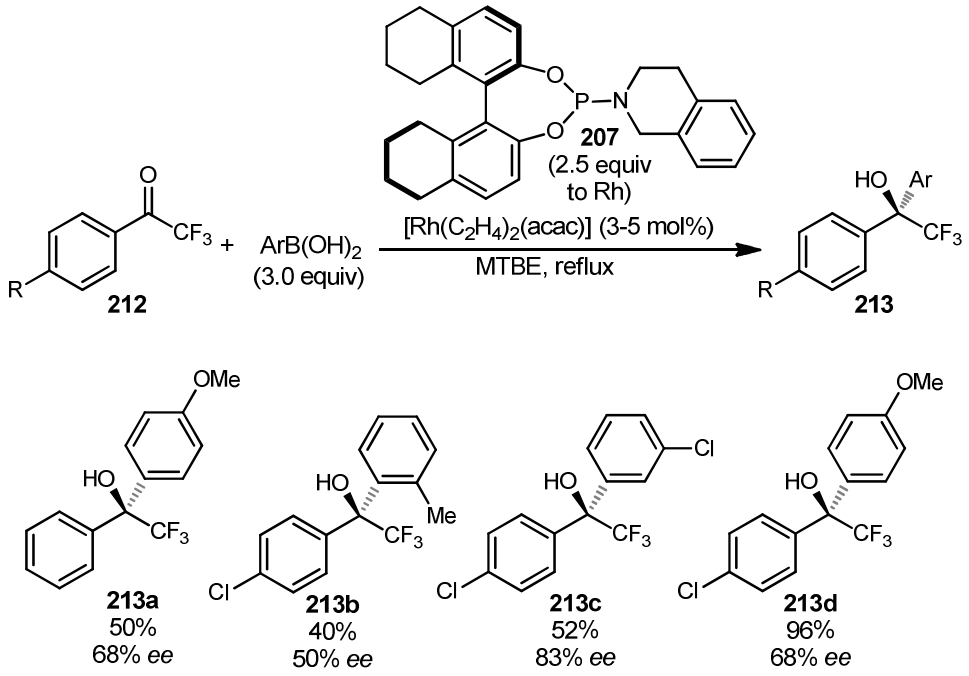
Equation 5.4

The other employs MeO-MOP as ligand and gives *ee*s of up to 91% (**Scheme 5.25**).[146]



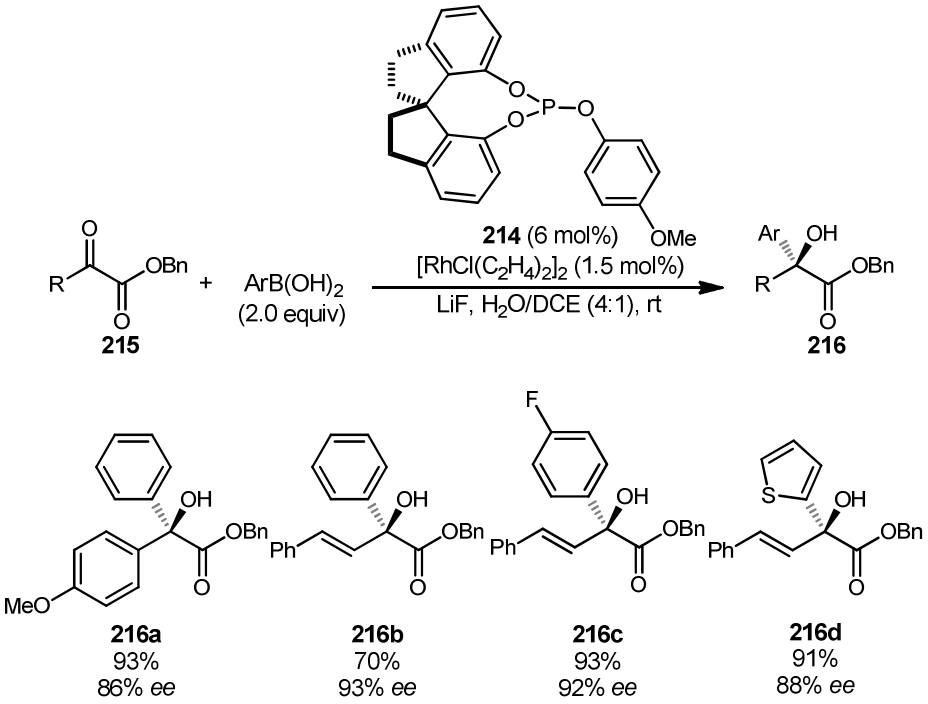
Scheme 5.25

Trifluoromethyl ketones have also been found to be reactive enough to undergo rhodium-catalysed arylations.[147] Again, a phosphoramidite was the ligand of choice. Ten examples are given with enantiomeric excesses ranging from 50 to 83% (**Scheme 5.26**).

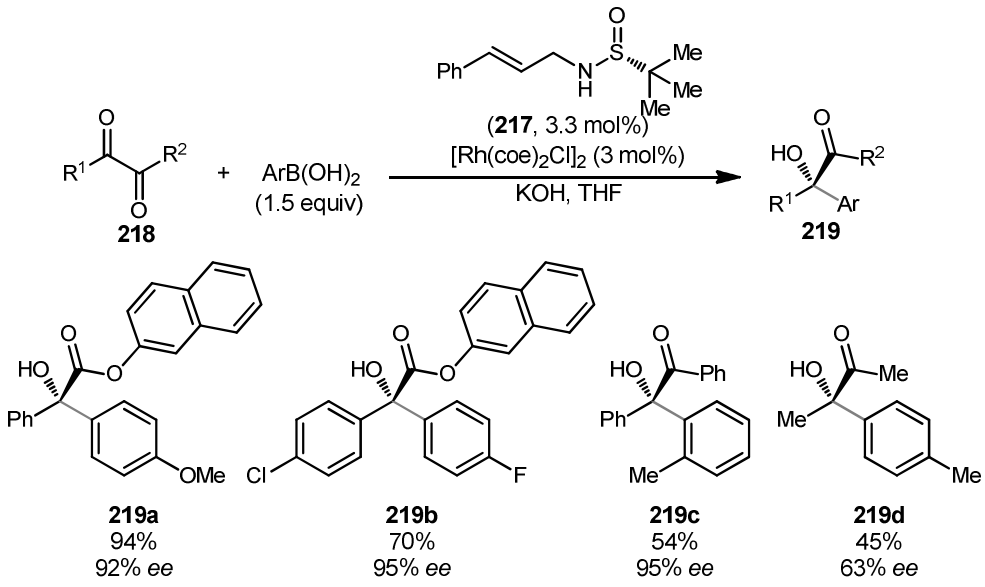


Scheme 5.26

α-Ketoesters have also been found to undergo rhodium-catalysed arylation with boronic acids in mostly excellent yields and high *ee*s (**Scheme 5.27**).[148] Spiromonophosphite ligands were employed and the products were shown to undergo smooth reduction and hydrolysis to give vicinal diols and α-hydroxy acids respectively. In 2012, another report of the asymmetric arylation of α-ketoesters and diketones was published.[149] A sulfur-olefin hybrid ligand (**217**) was used in the arylation of *α*-keto-naphthyl esters to give 21 examples all with *ee*s above 90% (**Scheme 5.28**). The enantiomeric excesses for diketones were also above 90% for aryl ketones, but there was some decrease when one or both of the ketones were aliphatic (e.g. **219d**).

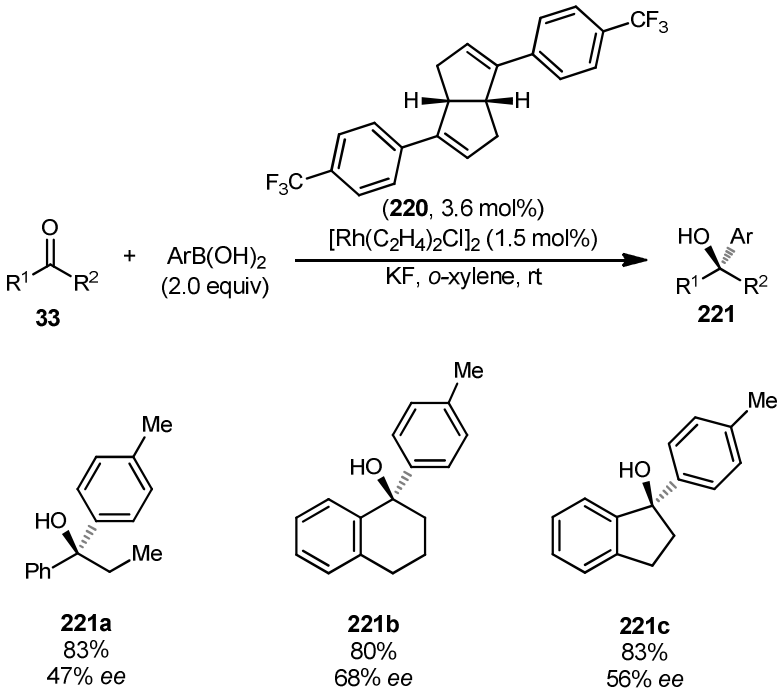


Scheme 5.27



Scheme 5.28

Very recently, the reaction of unactivated ketones has been described.[150] Anhydrous conditions were used with a diene ligand to give chiral tertiary alcohol products in up to 68% *ee* (**Scheme 5.29**).



Scheme 5.29

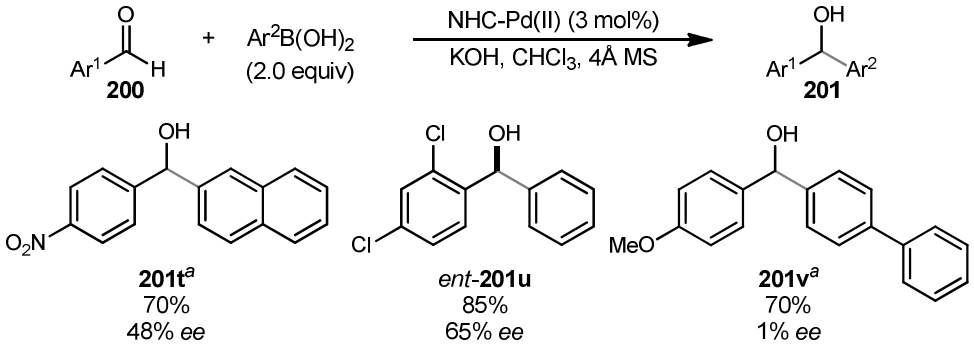
Whilst considerable success has been achieved in the arylation of carbonyl compounds under rhodium catalysis, there is still room for improvement in two main areas. Firstly, enantiomeric excesses are still variable, with aldehydes and unactivated ketones in particular often giving poor *ee* values. Secondly, the cost of rhodium limits the application of such chemistry in a commercial environment, especially on large scale. Therefore, there is a need to look at the asymmetric arylation of aldehydes using boronic acids catalysed by metals other than rhodium.

5.1.3 Asymmetric 1,2-Arylations of Aldehydes with Boronic Acids Catalysed by Metals Other than Rhodium

As well as rhodium, enantioselective arylation with boron nucleophiles have been reported using palladium, nickel, cobalt, copper and ruthenium catalysts.

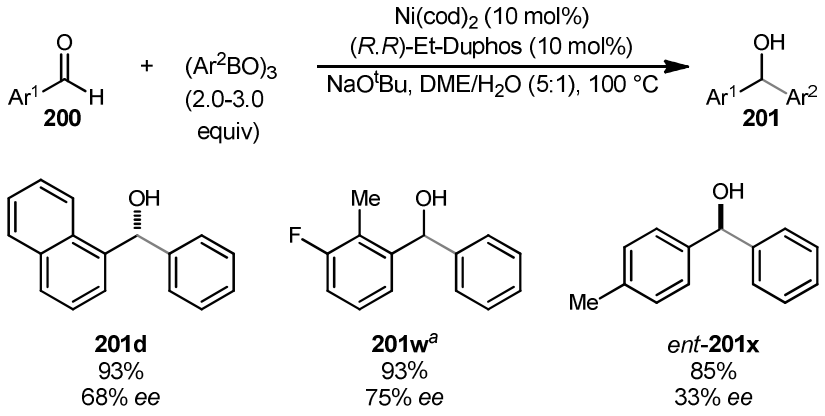
Palladium-catalysed additions of boronic acids to aldehydes were described by Ito in 2005.[151] However, an enantioselective version proved to be somewhat difficult to achieve. Chiral N-heterocyclic carbene (NHC) palladium complexes were tested by Shi in the arylation of benzaldehydes[152] and although yields were high, the enantiomeric excesses were

disappointing. The highest *ee* in the publication is 65%, but most examples are much lower (**Scheme 5.30**). The enantioselective palladium-catalysed arylation of aldehydes with boronic acids remains an unsolved problem.



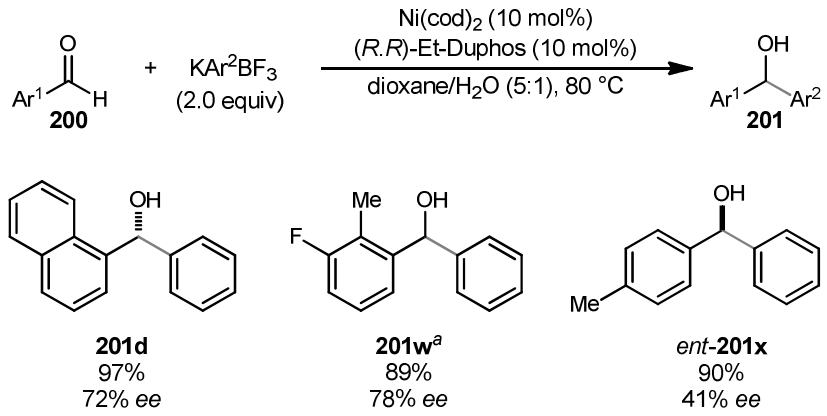
Scheme 5.30 [a]Absolute stereochemistry was not determined

The first example of an enantioselective nickel-catalysed arylation of aldehydes was reported by Aoyama in a communication in 2007[153] followed by a full paper in the following year.[154] The substrate scope was found to be broad when a range of arylboroxines were reacted with aromatic aldehydes, giving good yields. Enantioselectivities were in the range of 65-78% when (*R*,*R*)-Et-Duphos was employed as ligand for 2-substituted aromatic aldehydes. Unfortunately, when no *ortho*-substituent was present on the aromatic ring (e.g. **201x**), enantioselectivities were much lower (**Scheme 5.31**) and the opposite major enantiomer was obtained.



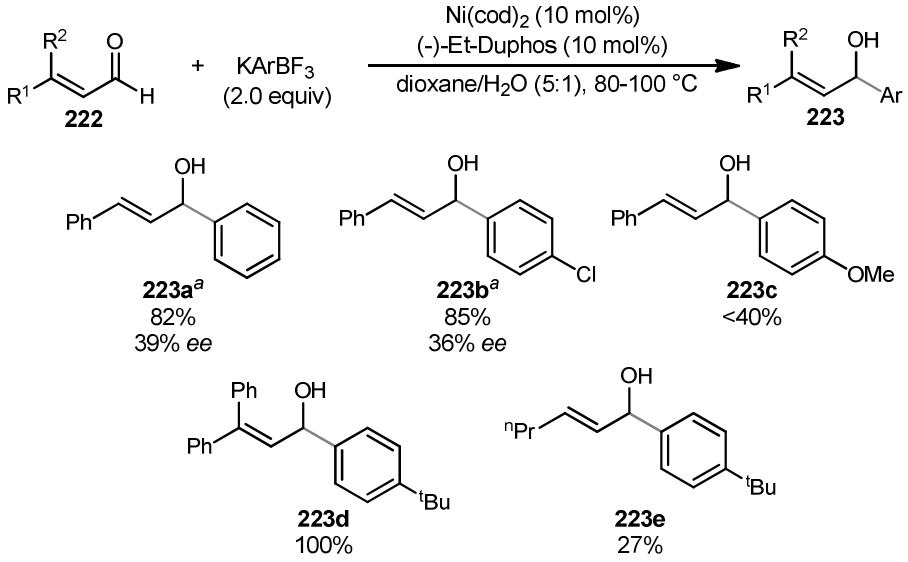
Scheme 5.31 [a]Absolute stereochemistry was not determined

Some improvement was observed when the aryl source was changed to potassium aryltrifluoroborates, although *p*-Me- and *p*-MeO-benzaldehydes still gave much poorer *ee*s than other substrates (**Scheme 5.32**).



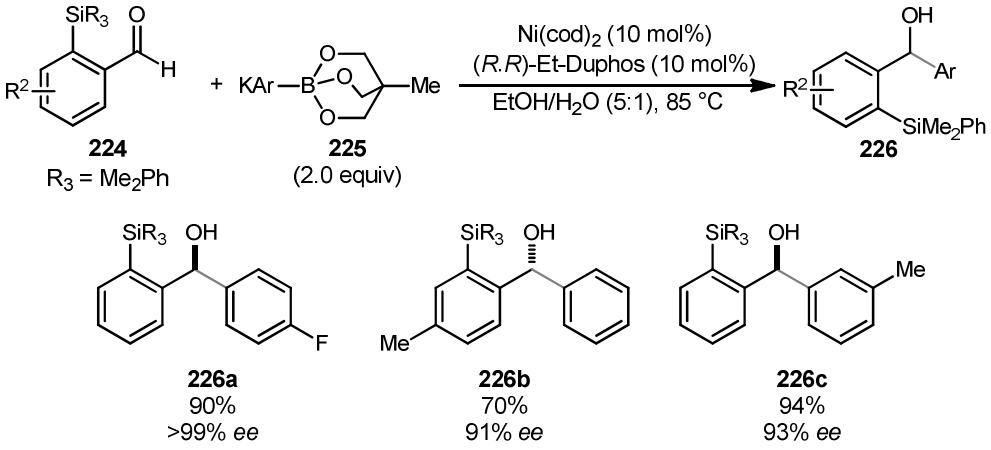
Scheme 5.32 [a]Absolute stereochemistry was not determined

The substrate scope was extended by the same authors in the following year to include *α,β*-unsaturated aldehydes,[155] which selectively underwent the 1,2-addition under optimised conditions (**Scheme 5.33**). A range of unsaturated aldehydes were arylated in good yields, with the exception of the reaction of *β*-aliphatic substrates which gave much lower values. Enantiomeric excesses are only reported for two of the products and these are both disappointing at 39% for **223a** and 36% for **223b**.



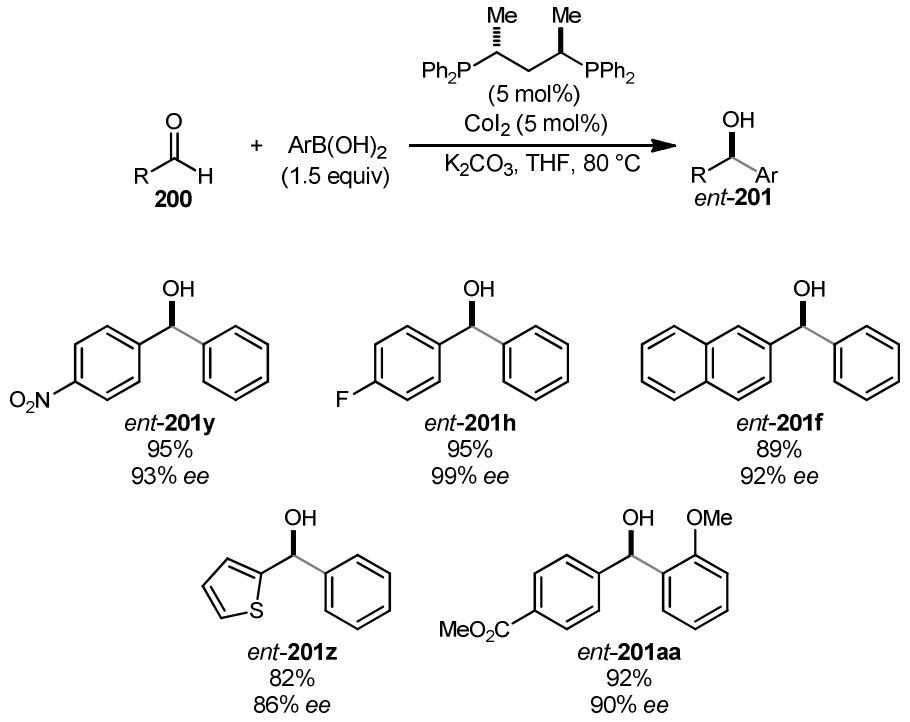
Scheme 5.33 [a]Absolute stereochemistry was not determined

A further publication in the same year details the group's attempts to increase the enantiomeric excesses for problematic benzaldehyde substrates, such as *p*-methylbenzaldehyde.[156] Their aim was achieved by the introduction of an easily removed dimethylphenylsilyl substituent into the *ortho*-position of the aldehyde and the use of aryltriolborates (**225**) as the arylating agent. All of the yields and enantiomeric excesses obtained were excellent (**Scheme 5.34**). Interestingly, reaction of the *p*-methyl-substituted substrate gave the opposite major enantiomer of product again. No reason is given for this.



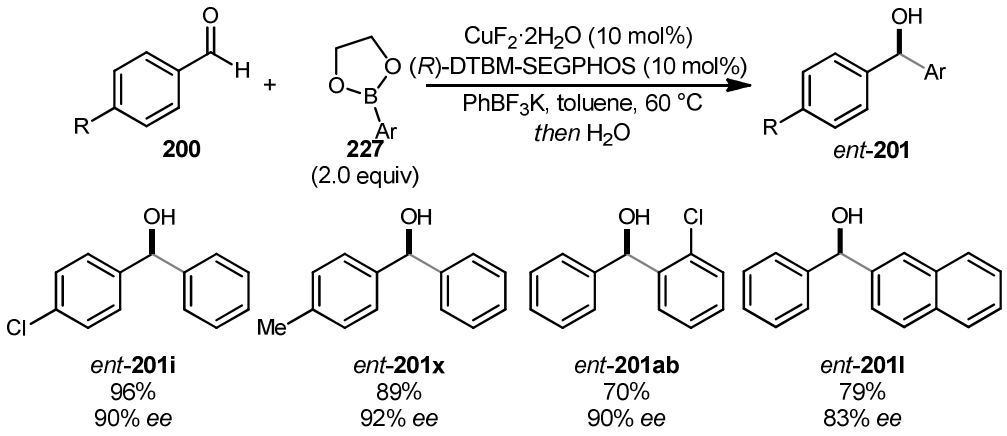
Scheme 5.34

Cobalt-catalysed arylations employing (*R*,*R*)-BDPP as ligand gave a range of diarylmethanol products in excellent yields with excellent *ee*s (**Scheme 5.35**).[157]



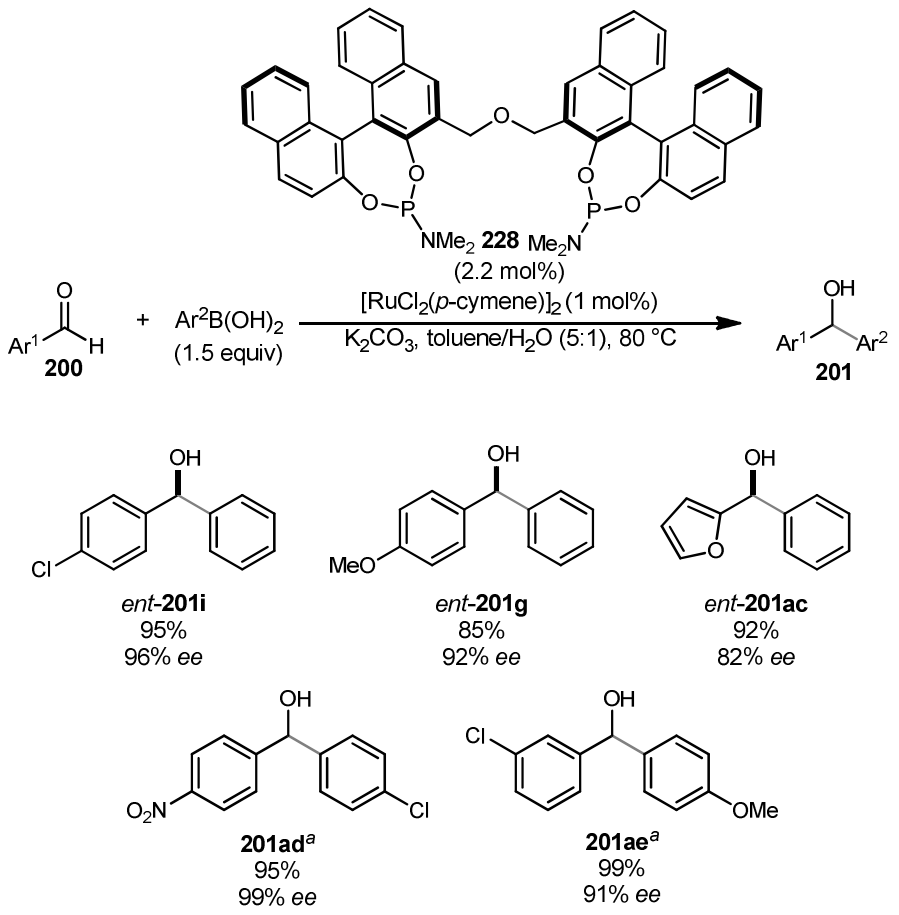
Scheme 5.35

Copper was first revealed as a cheap alternative to rhodium in the enantioselective arylation of aldehydes using boron species by Shibasaki in 2006.[158] $CuF_2 \cdot H_2O$ was used in conjunction with DTBM-SEGPHOS ligand to arylate benzaldehydes with the ethylene glycol ester of phenylboronic acid as the aryl source. An additive is required to obtain good yields and 15 mol% of $PhBF_3K$ was found to give the best results. The additive acts to speed up catalyst turnover. Only four examples of arylation were given, but yields and *ee*s were consistently high (**Scheme 5.36**).



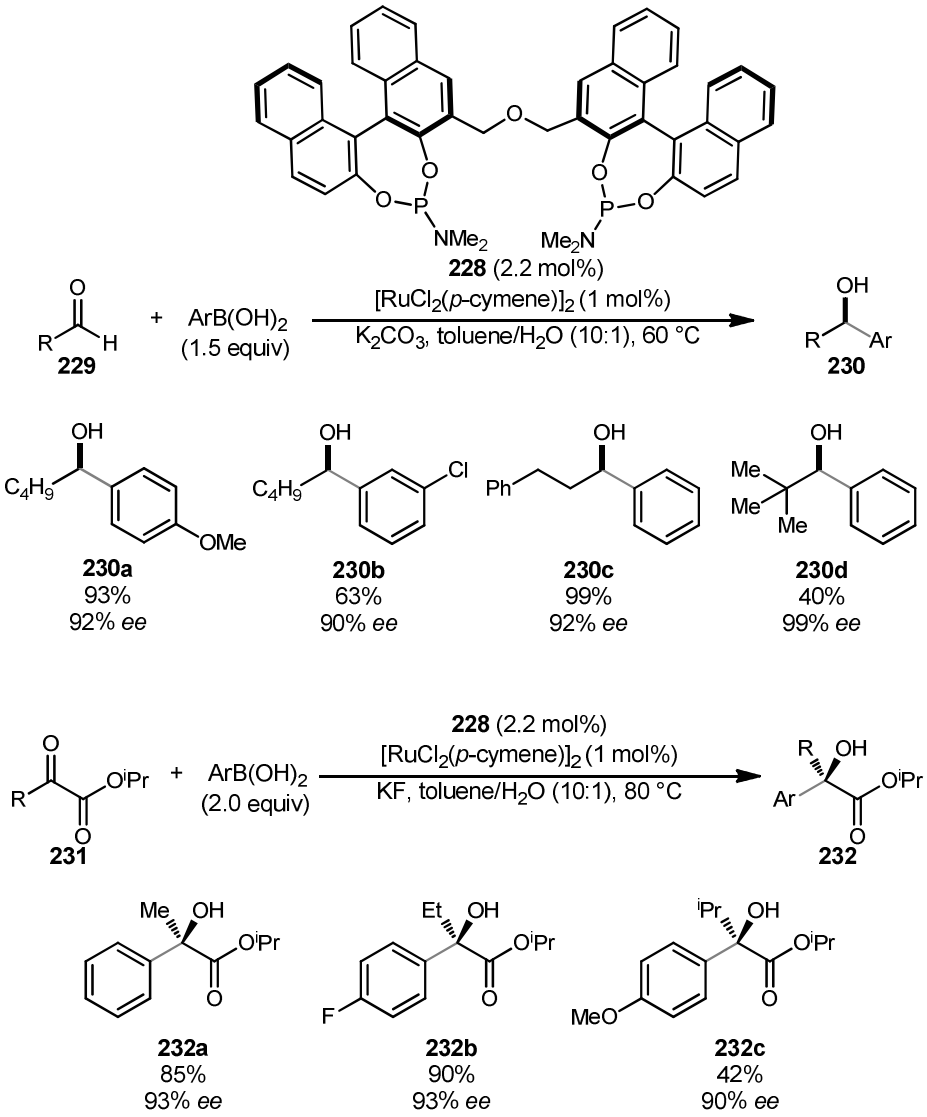
Scheme 5.36

Finally, there have been three reports of a very successful arylation of aldehydes under ruthenium catalysis by the group of Miyaura. In the first, a bidentate BINOL-derived phosphoramidite **228** was used as ligand to arylate a wide range of aromatic and heteroaromatic aldehydes.[159] The use of other ligands in this reaction gave significantly lower yields and *ee*s, which under their opimised conditions are excellent for 24 examples (**Scheme 5.37**).



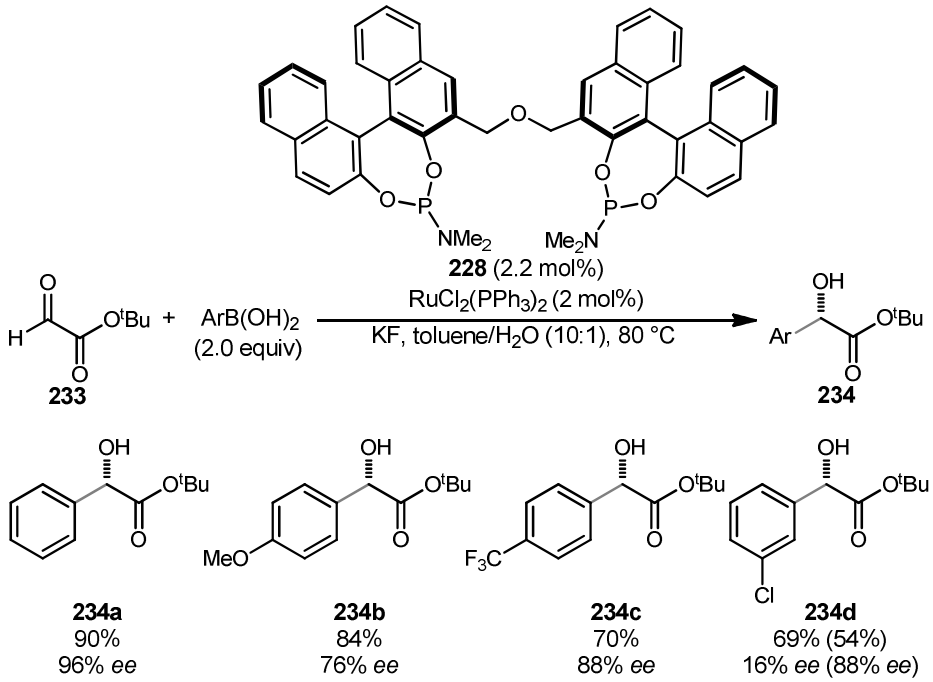
Scheme 5.37 [a]Absolute stereochemistry not determined

The O-linked-BINOL ligand **228** was also employed in the arylation of aliphatic aldehydes and ketoesters.[160] Enantiomeric excesses were excellent for all of the 39 examples although yields for the bulkier substrates are moderate (**Scheme 5.38**).



Scheme 5.38

The scope was extended to cover glyoxylate substrates.[161] Enantioselectivities were good to excellent for a number of substituted boronic acids, but an *ee* of only 16% was observed for reaction with 3-chlorophenyl boronic acid. This poor enantioselectivity was solved by the addition of methyldiphenylphosphine to the reaction mixture as an extra ligand. The methyldiphenylphosphine is believed to displace a triphenylphosphine ligand on the ruthenium centre, thus decreasing the hindrance around it and giving an *ee* of 88% (**Scheme 5.39**).



Scheme 5.39 [a]Values in parenthesis are those obtained with $PMePh_2$ (2.2 mol%) as an additive.

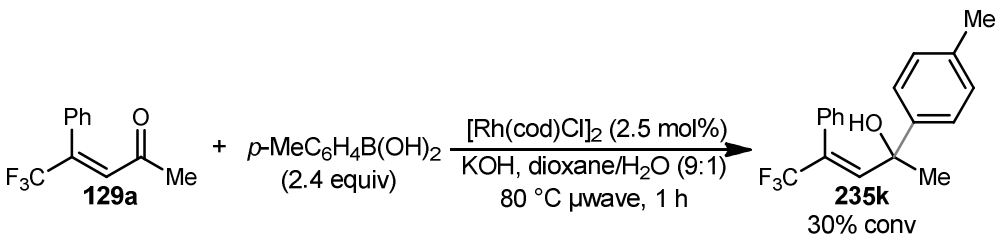
In summary, rhodium-catalysed arylations are a powerful method for the enantioselective synthesis of both carbonyl compounds with a β-stereocentre and diarylmethanols. There is also a need for development of similar methods which employ cheaper metals than rhodium.

5.2 Results and Discussion

The asymmetric formation of carbon–carbon bonds is of great importance throughout organic chemistry. As we have seen, the metal-catalysed reaction of conjugate acceptors with boronic acids is an excellent approach. As such, the utility of such methodology in the reaction of *β*-fluoroalkyl-*α*,*β*-unsaturated carbonyl compounds deserves thorough investigation.

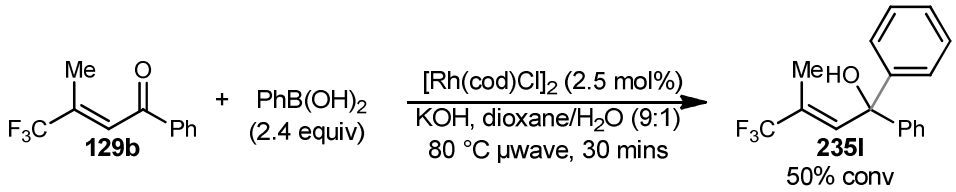
5.2.1 Enantioselective Metal-Catalysed Arylations of *β*-Fluoroalkyl-*α*,*β*-Unsaturated Ketones and Esters

With a number of *β*-fluoroalkyl enones in hand from our previous endeavours (see **Chapter 4.2.1**), we embarked upon an investigation into the reaction of such compounds under conditions commonly employed for conjugate arylations. Rhodium was selected for early experimentation due to the significant prominence of this metal in enantioselective conjugate arylation chemistry. Compound **129a** was subjected to reaction with *p*-tolylboronic acid in the presence of $[Rh(cod)Cl]_2$ (2.5 mol%) and KOH (2.5 equivalents) in dioxane/H_2O (9:1) under microwave irradiation at 80 °C (**Equation 5.5**). As we have seen, there are limited examples of the reaction of ketones in rhodium-catalysed arylations, so it was somewhat surprising that 30% conversion to the product of 1,2-arylation was observed. The remainder was unreacted starting material and none of the extremely hindered product of conjugate addition (bearing an all-carbon quaternary stereocentre) was observed.



Equation 5.5

Subjecting a further substrate, **129b**, and phenyl boronic acid to the same conditions for 30 minutes gave 50% conversion to the direct hydroarylation product (**Equation 5.6**).



Equation 5.6

Although not the intended products, the compounds obtained by this reaction are chiral allylic alcohols, which could also be used in further transformations as a useful enantioenriched fluoroalkylated building block. Therefore, screening to obtain conditions for an enantioselective version of this reaction was undertaken. For enantioselective reactions, $[Rh(C_2H_4)_2Cl]_2$ was employed as catalyst due to the greater lability of the ethylene ligands relative to COD, which allows for the more rapid formation of the rhodium-chiral ligand complex.

Initially, the use of chiral diene ligands was investigated, as these have been shown to give high enantiomeric excesses in the reaction of a range of substrates in rhodium-catalysed arylations with boronic acids. However, in this case, they were found not to be the best class of ligand and conversions obtained were very poor (**Table 5.1**) with only one ligand (**189b**) giving any desired product at all (8% conversion). The remainder of the reaction mixture was mostly starting material, although with some of the dienes, a small amount of double bond isomerisation was observed (<5%). As a result of the very low conversions, enantiomeric excesses were not measured for these reactions.

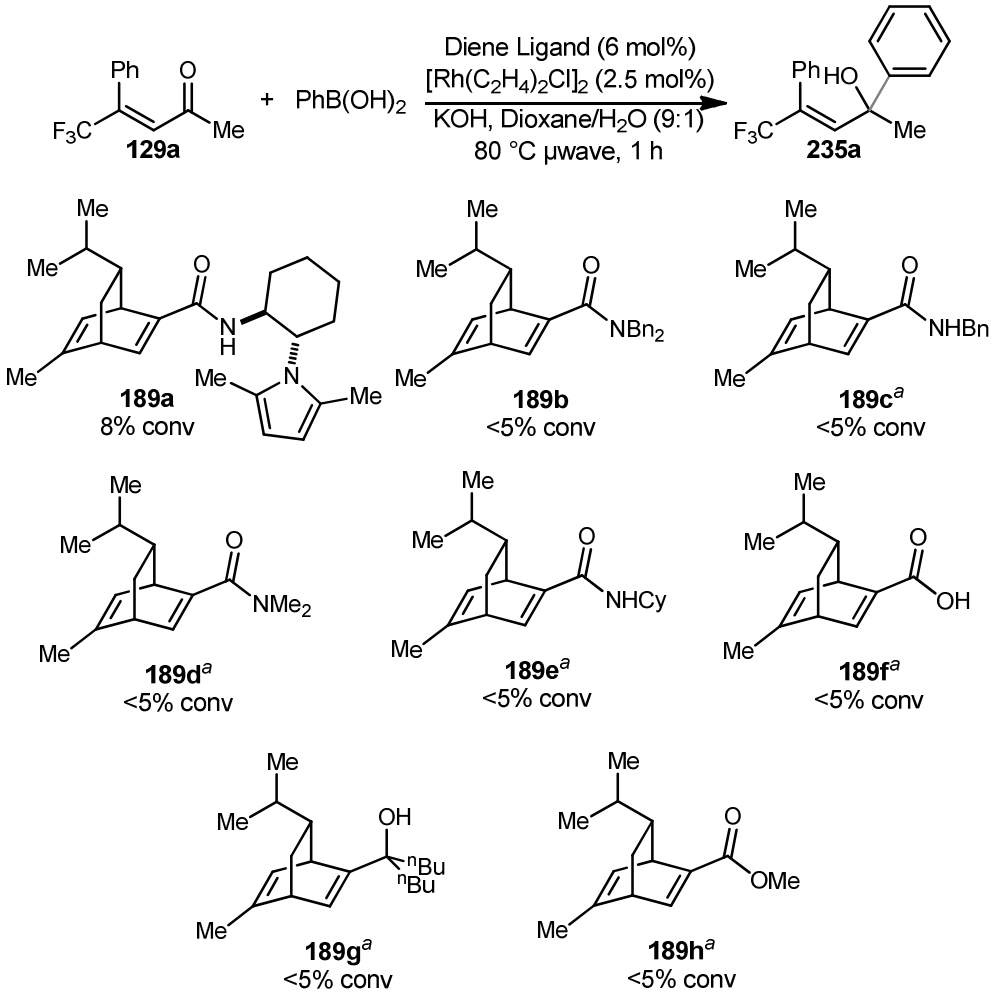
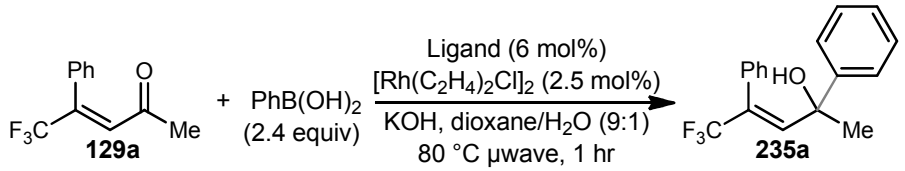
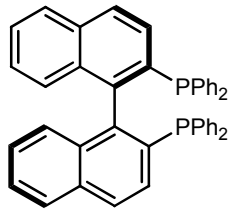


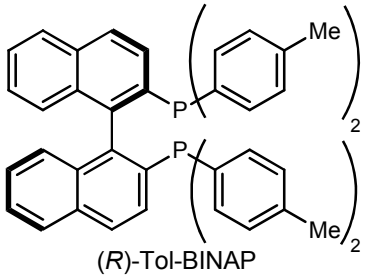
Table 5.1 Ligands synthesised by Benoit Gourdet, Iain Roy and Aarkarsh Saxena. [a]Result obtained by Graham Pattison

The use of chiral bisphosphine ligands was immediately shown to be more promising, with several ligands giving moderate to good conversions. Selected examples of the ligands screened are shown in **Table 5.2**. As a result of this screening, two ligands were identified as showing potential for further optimisation and it is these that formed the basis of later research. (*R*,*R*)-MeDuPhos gave almost complete conversion to the desired product after an hour at 80 °C, although the enantiomeric excess required improvement at only 44%. (*S*)-MeO-BIPHEP gave the highest enantiomeric excess obtained, at 76%, but for this ligand the conversion was a disappointing 29% under these conditions. In most cases, increasing the steric bulk of the ligand employed resulted in a significant decrease in conversion to the desired product. For example, when (*R*,*R*)-^{i}Pr-DuPhos was used, only a trace of product was obtained.

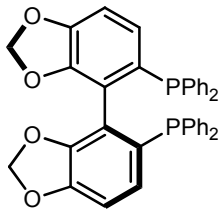




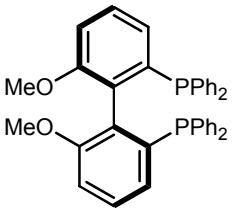
(*R*)-BINAP
23% conv
64% *ee*



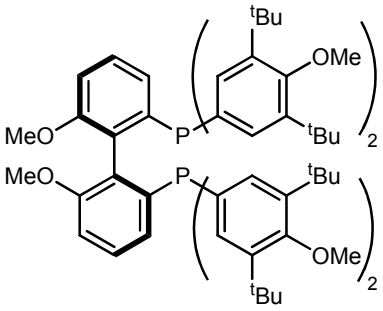
(*R*)-Tol-BINAP
< 5% conv



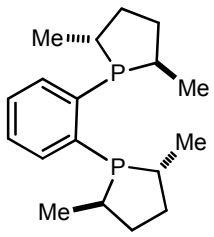
(*S*)-SEGPHOS
< 5% conv



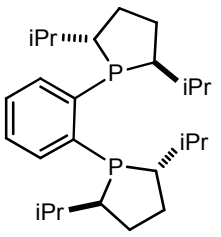
(*S*)-MeO-BIPHEP
29% conv
76% *ee*



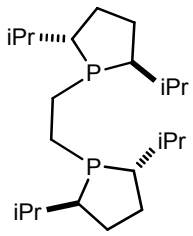
(*S*)-3,5-^{t}Bu,4-MeO-MeOBIPHEP
36% conv
30% *ee*



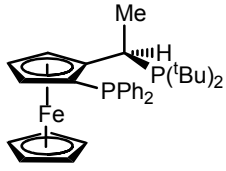
(*S*,*S*)-MeDuPhos
97% conv
44% *ee*



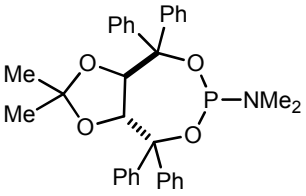
(*S*,*S*)-^{i}PrDuPhos
< 5% conv



(*S*,*S*)-^{i}Pr-BPE
60% conv
46% *ee*



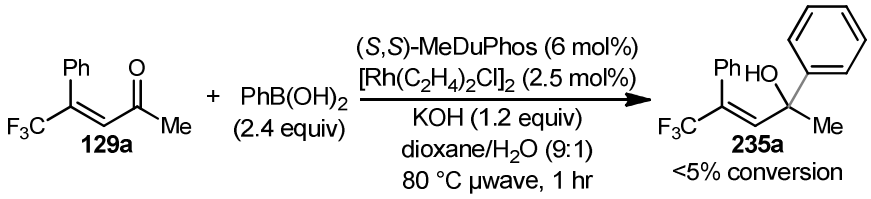
Josiphos, SL-J001-1
50% conv
6% *ee*



TADDOL-Phosphoramidite[a]
14% conv
32% *ee*[b]

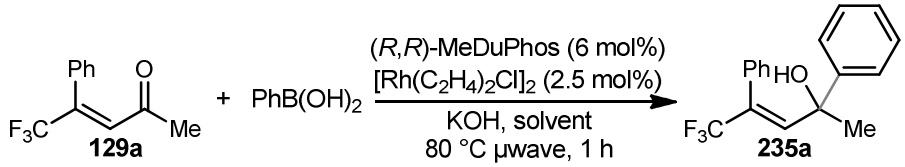
Table 5.2 [a]12 mol% ligand employed. [b]Major enantiomer obtained opposite to that obtained for (*R*)-BINAP.

Firstly, the effect of temperature on the reaction using (*S*,*S*)-MeDuPhos was investigated. Unfortunately, decreasing the temperature below 80 °C led only to decreased conversions with no significant improvement to the enantiomeric excesses. Decreasing the amount of base employed to 1.2 equivalents resulted in only a trace of product being formed.



Equation 5.7

Solvent screening was carried out next (**Table 5.3**). For most of the solvents tried, no more than a trace of product was formed and the reactions were very messy with a number of side products observed, including those of double bond isomerisation and reduction. THF gave a decreased conversion compared to dioxane and the *ee* was slightly lower (38%). There was no starting material remaining when methanol was used as solvent, but there was 31% of an unidentified side product and the *ee* was not improved. Trifluorotoluene also resulted in no remaining starting material being observed, but there was no desired product either. After the solvent screening was completed, dioxane remained the preferred solvent.



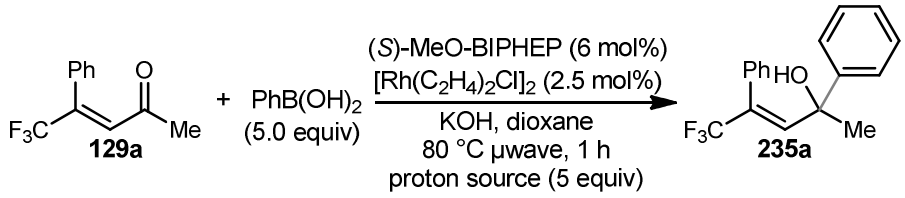
Solvent	Desired Product (%)	ee (%)
dioxane/water (9:1)	97	44
Water	<5	–
THF/water (9:1)	51	38
DCE/water (9:1)	<5	–
Methanol	69	42
acetonitrile/water (9:1)	<5	–
heptane/water (9:1)	<5	–
trifluorotoluene/water (9:1)	<5	–
MTBE/water (9:1)	<5	–

Table 5.3

The use of other boron-based aryl sources was also explored with (*R*,*R*)-MeDuPhos as ligand, including boronic esters, sodium tetraarylborate salts and potassium trifluoroborates. Out of these, only the boronic ester gave any product and the conversion here was a disappointing 25%.

As no improvement in enantioselectivity had been observed after extensive screening with (*R*,*R*)-MeDuPhos as ligand, our hopes then rested on increasing the conversions obtained with (*S*)-MeOBIPHEP as ligand, which gave a 76% *ee* during ligand screening, but only a 29% conversion.

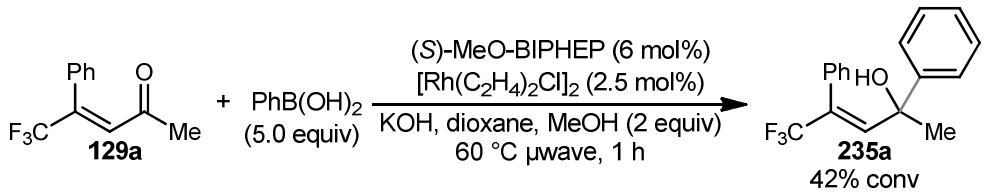
Increasing the amount of boronic acid employed to 5 equivalents gave no improvement to the conversion when water was used as part of the solvent mixture (9:1 with dioxane). However, when only 5 equivalents of water were employed along with 5 equivalents of boronic acid, the conversion to desired product increased to 40 % (**Table 5.4**). Switching the proton source to methanol (5 equiv) gave 51% conversion. Bulkier alcohols, such as ^{t}butyl alcohol resulted in only 5% product formation or less.



Proton Source	Desired Product (%)
Water	40
Methanol	51
^{t}Butanol	<5

Table 5.4

Decreasing the reaction temperature (with the aim of decreasing the rate of protodeboration of the boronic acid) to 60 °C gave only 10% conversion, which increased to 42% when the amount of methanol was reduced to 2 equivalents (**Equation 5.8**).



Equation 5.8

As a major limiting factor in the conversions of these reactions is the protodeboration of boronic acids, further screening was conducted with the aim of decreasing the amount of protodeboration. Bases other than KOH and different quantities of base were explored. No

improvement to the conversions was observed and a significant decrease was seen when the equivalents of base were dropped below two. Lewis acids, including diethylzinc, aluminium triflate, and titanium tetrachloride, were also tested in place of base, but no desired product formation was observed.

Addition of furthur equivalents of boronic acid after 30 minutes reaction time and the slow addition of the boronic acid by syringe pump over the course of one hour resulted in no improvement and in the case of the slow addition, actually led to a decrease in the amount of desired product formed.

Other rhodium sources were also tested including rhodium acetate and cationic rhodium catalysts, but once again none of these offered any improvement to the conversions. Finally, variations in reaction times, heating methods (thermal *versus* microwave irradiation) and concentration were explored.

The best results obtained are shown in **Table 5.5** along with the scope. The less sterically hindered methyl ketones offer the best conversions and enantiomeric excesses which are comparable to much of the existing literature. The lower *ee*s for more hindered ketones (**235d**, **235f** and **235g**) are presumably a result of decreased steric discrimination of the two sides of the carbonyl compound. The best result was obtained for the heptafluoropropyl substrate.

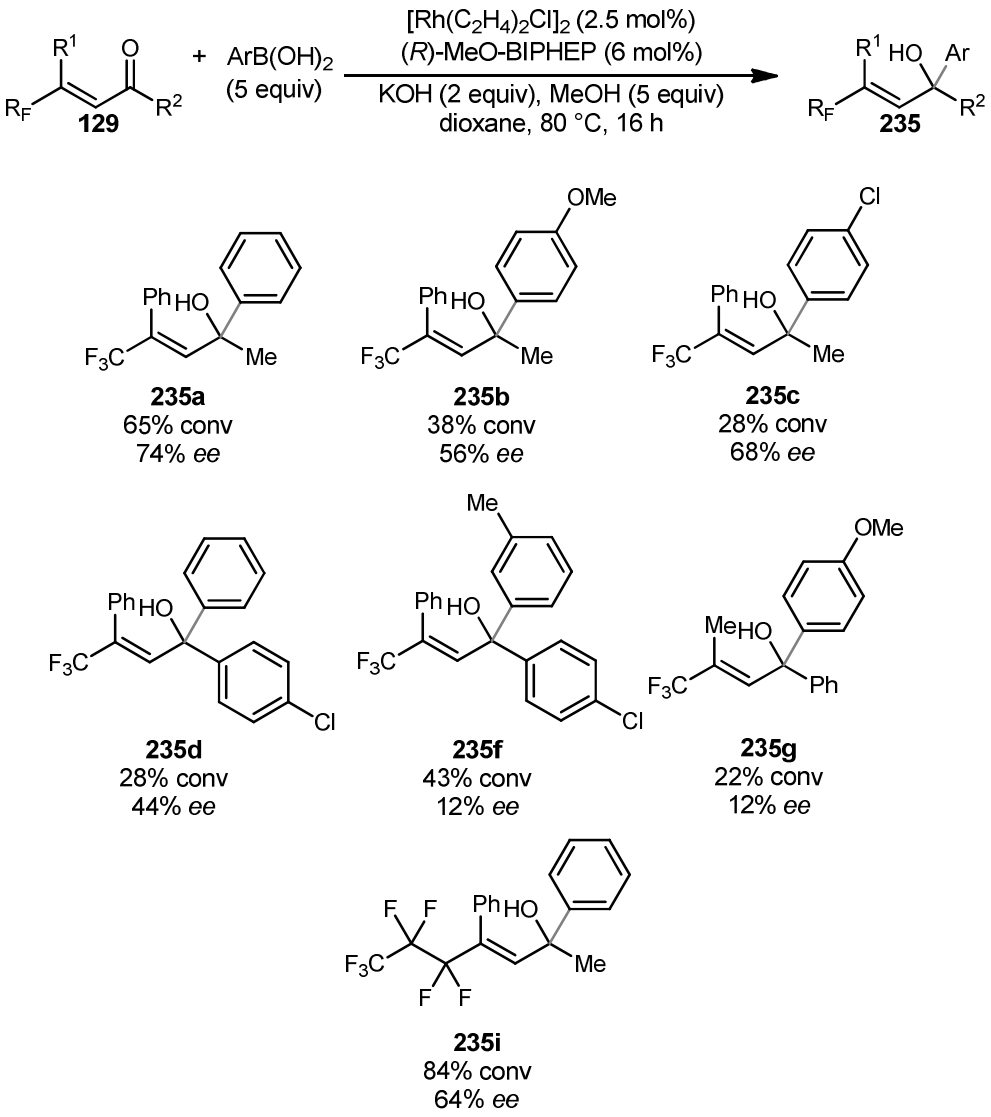
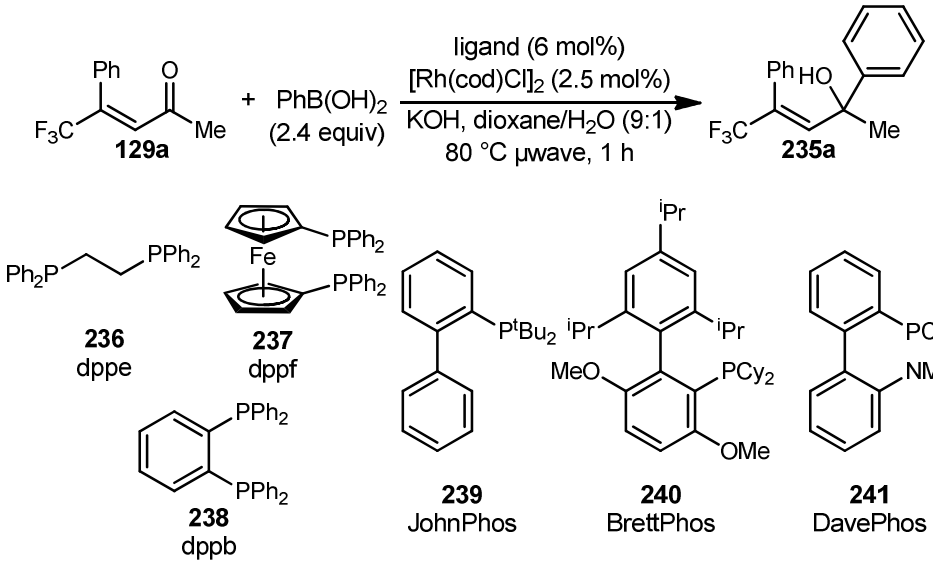


Table 5.5

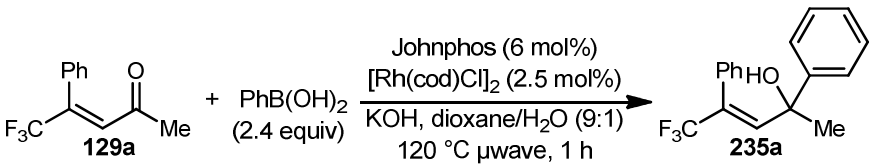
In addition to the enantioselective reaction, we also sought to optimise a set of racemic conditions for the arylation of *β*-fluoroalkyl-*α*,*β*-unsaturated ketones. The initial conversion with no ligand present was 33% using $[Rh(cod)Cl]_2$, KOH and 2.4 equivalents of boronic acid. Screening of racemic ligands was then conducted and the results are shown in **Table 5.6**.



Ligand	Conversion (%)
Dppe	20
Dppf	12
Dppb	33
PCy_3	15
Johnphos	40
Brettphos	31
Davephos	40

Table 5.6

Furthur screening of concentrations, temperatures and reaction times failed to increase the observed conversions above 46% (achieved with Johnphos when the temperature was increased to 120 °C for one hour, **Equation 5.9**).



Equation 5.9

Fortunately, it was discovered that switching the aryl source from phenylboronic acid to sodium tetraphenylborate gave complete consumption of starting materials after one hour heating at 80 °C under microwave irradiation. The scope is shown in **Table 5.7**. The reaction gives moderate to good yields for a range of substrates. The yield was substantially lower for the introduction of the *p*-chlorophenyl group (**235c**) despite the use of higher temperature, presumably due to the lower reactivity of electron-deficient borates. The reaction was found

to be particularly poor for the substrate containing a deactivating *p*-MeO-phenyl ketone (**235h**). In this case, some of the product of 1,4-arylation (16%) was also observed as well as unreacted starting material (16%). Only 6% conversion was seen for the arylation of **129a** with bulky sodium tetranaphthylborate to give **235j**.

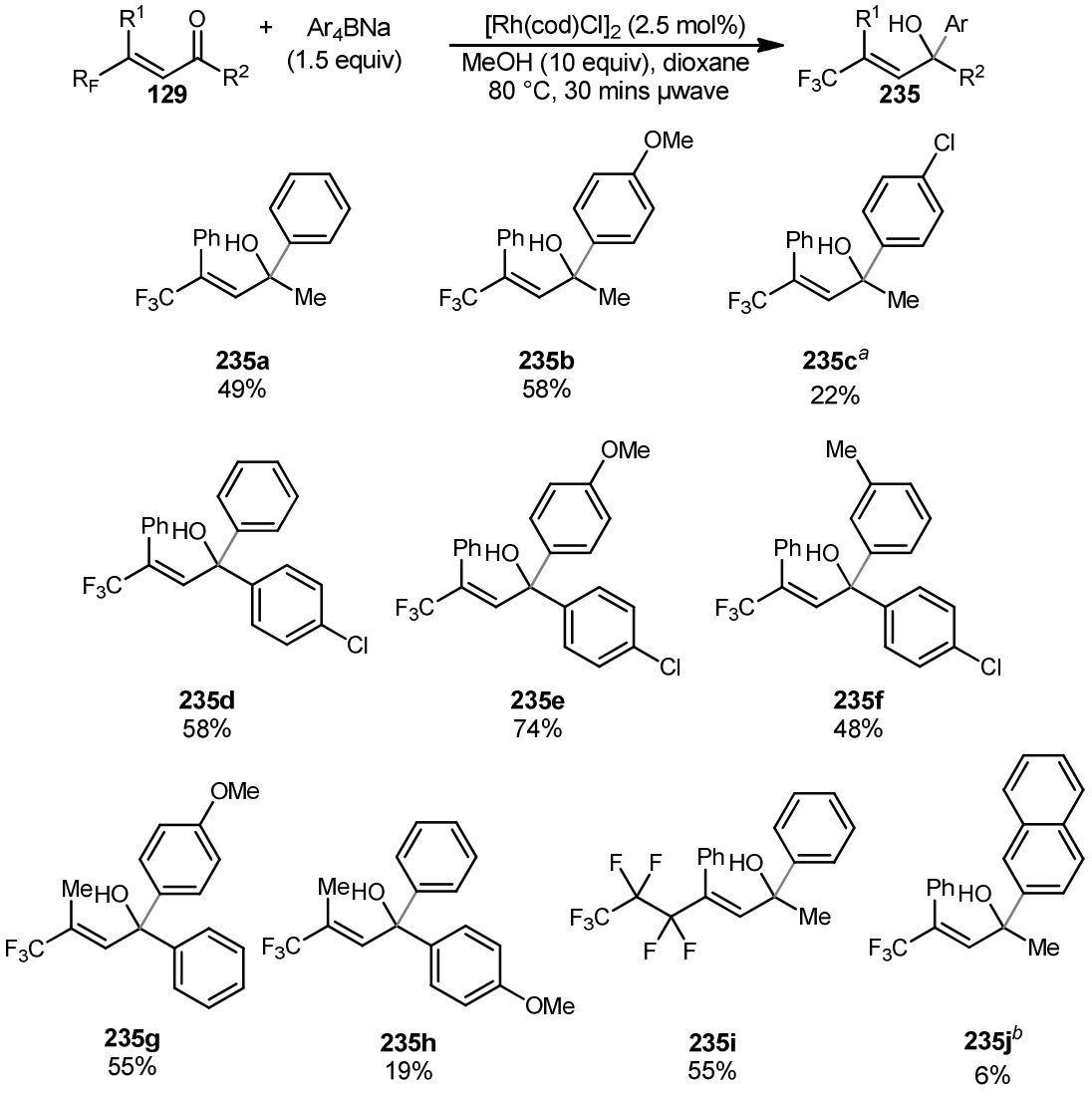
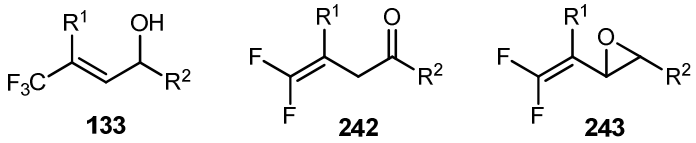


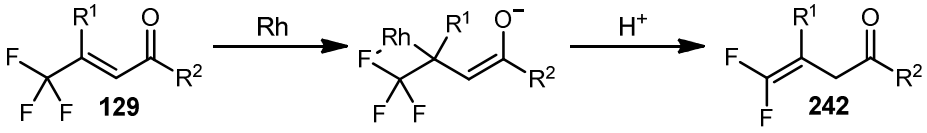
Table 5.7 [a]Reaction carried out at 120 °C [b]NMR conversion

Whilst there was no starting material remaining in these reactions, the isolated yields were modest due to the amount of side product formation. There were up to 14 side products observed in these reactions and those which have been identified are shown in **Scheme 5.40**.



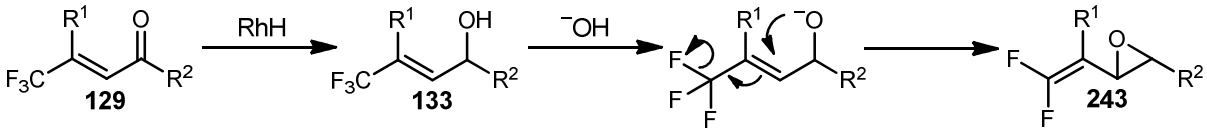
Scheme 5.40

Compound **133** is the product of a 1,2-reduction. It seems likely that this was formed by the reaction of the enone starting material with rhodium-hydride. However, it is not known how the rhodium-hydride forms under the reaction conditions. Compound **242** is the product of overall hydrogen fluoride elimination. It is feasible that this could occur as given in **Scheme 5.41**. The proposed mechanism involves a similar sequence of events to that given earlier for the Cu-F interaction (see **4.2.1**), but involving rhodium instead of copper.



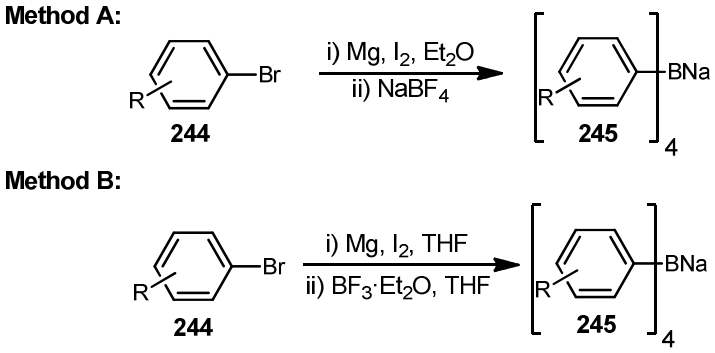
Scheme 5.41

Compound **243** could be formed by the intramolecular attack of the oxygen anion of deprotonated **133** upon the alkene moiety, eliminating a fluoride (**Scheme 5.42**).



Scheme 5.42

Only sodium tetraphenylborate is commercially available, so most of the other tetraarylborate salts were synthesised using Method A shown in **Scheme 5.43**. This method of synthesis fails for bulkier aryl groups, such as *o*-tolyl or naphthyl. In these cases, Method B was used.



Scheme 5.43

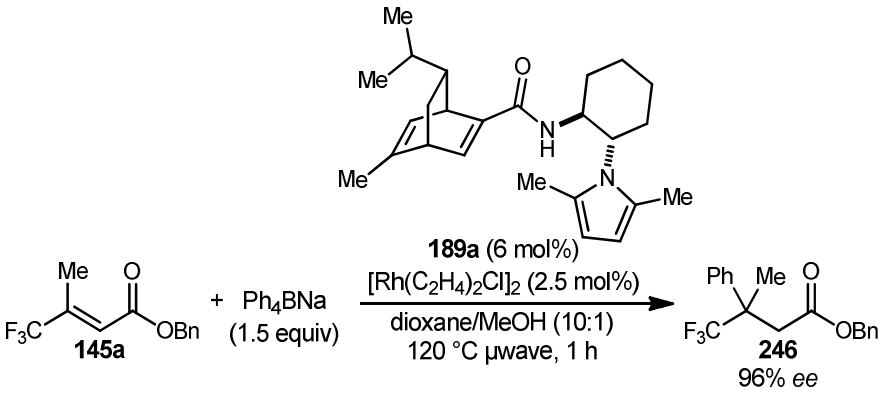
The success of tetraarylborate salts in the racemic reaction encouraged us to re-explore the use of these as an aryl source in the enantioselective version. Unfortunately, the use of $[Rh(C_2H_4)_2Cl]_2$ with a range of ligands and sodium tetraphenylborate gave no product formation. Switching back to $[Rh(cod)Cl]_2$ as catalyst and adding chiral ligands led to decreased conversions compared to the ligand-free reaction and no enantioselectivity was observed.

Finally, we investigated the use of metals other than rhodium in the enantioselective arylation of *β*-fluoroalkyl-*α*,*β*-unsaturated ketones. Despite the screening of a broad range of conditions employing manganese, iron, cobalt, nickel, copper, ruthenium, palladium, silver, iridium, platinum, gold and indium, no desired product was observed for reaction with any metal other than rhodium. Iridium gave 10-20 % of 1,2-reduction product and other metals mostly returned starting materials only. (The screening of other metals was carried out in collaboration with Graham Pattison.)

We have seen that the arylation of *β*-fluoroalkyl-*α*,*β*-unsaturated ketones gives the product of a 1,2-addition to the carbonyl group rather than the more usual 1,4-addition. It was expected that the reaction of *β*-trifluoromethyl-*α*,*β*-unsaturated esters, on the other hand, would give the product of conjugate addition. However, it was also likely that harsh conditions would be required to generate the very hindered quaternary stereocentre bearing a fluoroalkyl group. Nevertheless, as success in the development of suitable conditions would lead to a method for the synthesis of compounds currently difficult to access, endeavours in this area are desirable.

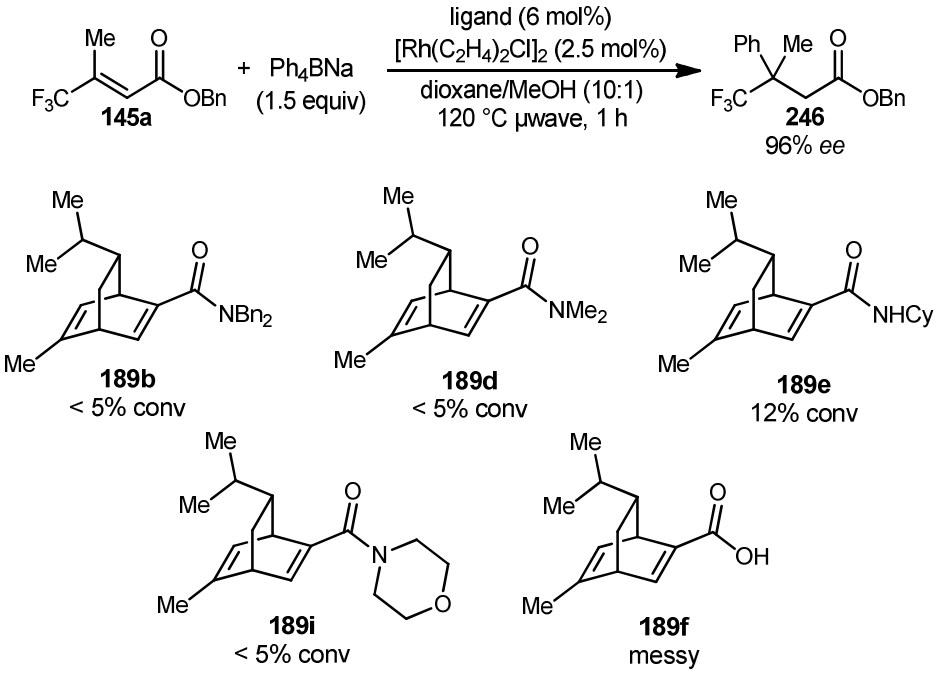
Initial attempts employing boronic acids gave no product under a range of racemic conditions tested. Boroxines were also unsuccessful. However, the use of sodium tetraarylborate salts,

which have been previously reported in arylations to give quaternary stereocentres,[128] gave better results. With $[Rh(cod)Cl]_2$, a conversion of 25% was obtained after 45 minutes heating at 80 °C under microwave irradiation. We then sought to obtain enantioselective conditions through the addition of a chiral ligand to the reaction mixture. Heating under microwave irradiation at 120 °C for an hour in the presence of diene ligand **189a** gave 88% conversion to the desired product with an enantiomeric excess of 96% (**Scheme 5.44**). Unfortunately, the reaction lacks reproducibility and further repeats have given vastly differing conversions (some as low as 33%), although the *ee* remains at 96%.



Scheme 5.44

Other diene ligands were screened with the hope of selecting one that gives better and more consistent conversions to desired product. The results are given in **Scheme 5.45**. The only other ligand that gave more than a trace of desired product was the monocyclohexylamine diene **189e** and the reaction mixture in this case was very messy with a large number of side products.



Scheme 5.45 Ligands were synthesised by Benoit Gourdet, Iain Roy and Aarkarsh Saxena

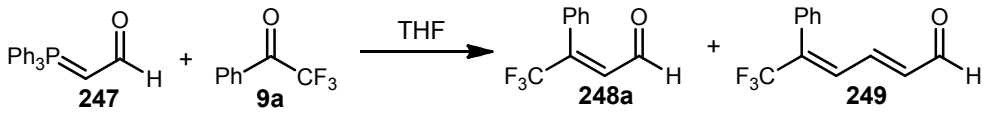
So far, no improved conditions for the conjugate arylation of *β*-trifluoromethyl-*α*,*β*-unsaturated esters have been found. It seems likely that a radically different approach is required to achieve successful conditions for such a challenging transformation.

At this point a decision was made to investigate the reactions of more reactive substrates: *β*-fluoroalkyl-*α*,*β*-unsaturated aldehydes.

5.2.2 Enantioselective Metal-Catalysed 1,2-Arylations of *β*-Fluoroalkyl-*α,β*-Unsaturated Aldehydes

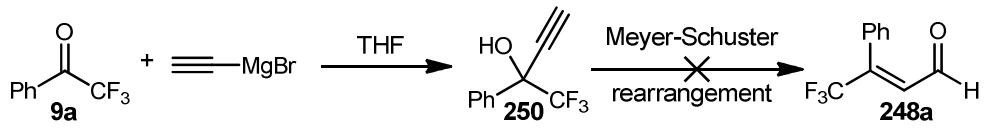
The greater reactivity of aldehydes relative to ketones was expected to increase the conversion to the product of 1,2-arylation. The allylic alcohols thus obtained could then be used as chiral fluorinated building blocks for furthur elaboration into a range of structures.

The first challenge encountered was the synthesis of these new substrates. Initial attempts focused on the direct formation of the enal through a Wittig reaction in the exact same manner as used for the ketones (**Scheme 5.46**). Unfortunately, a number of problems arose with this method. The first attempt gave good stereoselectivity with a 17:1 ratio of *E* to *Z*, but also gave a substantial amount (approximately 50% of the reaction mixture) of **249**. This was formed by the reaction of the initial product with a further molecule of ylide. Additionally, the isolated yield was disappointing (48% for both products combined). In an attempt to minimise the formation of **249**, the reaction was repeated at a lower concentration. This change decreased the amount of **249** to 30%, but gave poorer stereoselectivity (<9:1 *E*:*Z*). Attempts to separate these isomers by column chromatography not only failed, but also revealed the low isolated yields achieved earlier to be the result of instability of the aldehyde major isomer on silica. The double bond geometries were assigned using $^{1}H–^{19}F$ HOESY as before.



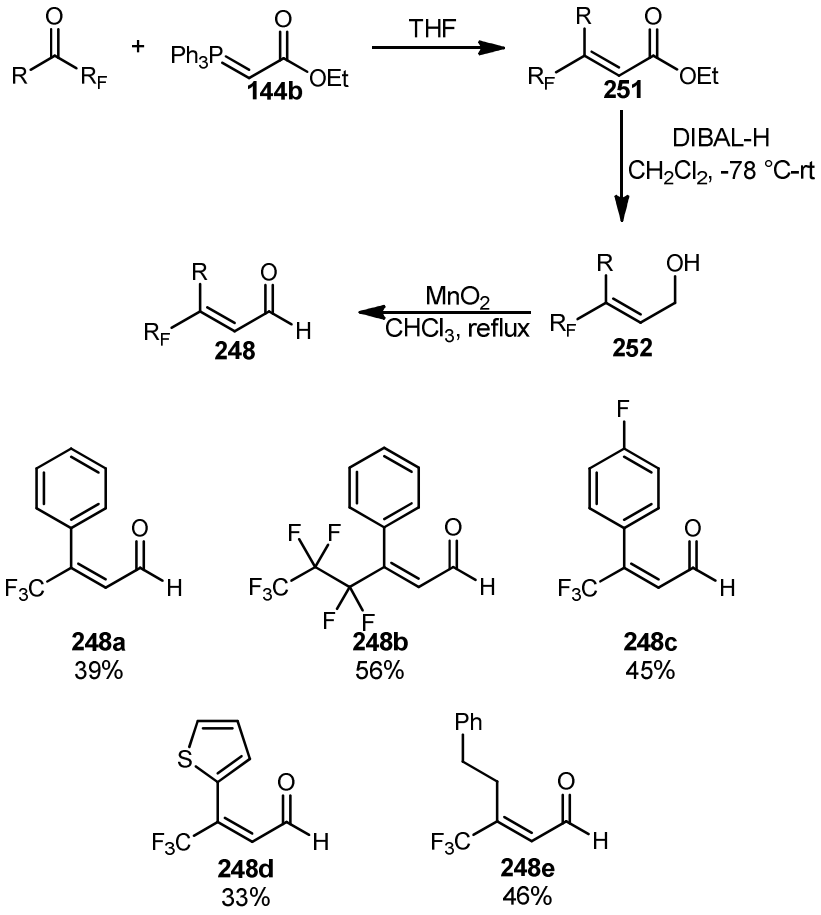
Scheme 5.46

A new approach to the synthesis was sought. The application of a Meyer-Schuster reaction was explored (**Scheme 5.47**), although no product was observed under a range of conditions based on literature precedent, such as the use of indium trichloride[162] and the combination of molybdenum, gold and silver.[163]



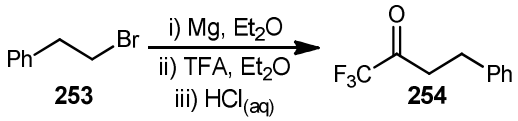
Scheme 5.47

A more successful approach was developed by synthesising the *α*,*β*-unsaturated ethyl esters, reducing these with DIBAL to give allylic alcohols (**252**) and then oxidising the alcohols with manganese dioxide to give the desired aldehydes (**Scheme 5.48**). Advantages to this approach are the separability of the *E*/*Z* isomers at the ester stage and lack of purification required for the aldehyde product. Simply filtering the reaction mixture through celite gave clean *α*,*β*-unsaturated aldehydes which were used directly in the arylation reactions. **Scheme 5.48** shows the aldehydes that were made using this approach. The *α*,*β*-unsaturated aldehydes were found to be stable at room temperature for up to four weeks, but would last for up to three months when stored at, or below, 0 °C. The exception to this is **248b**, which degraded much more quickly and was therefore stored as the allylic alcohol and oxidised immediately prior to use in the arylation.



Scheme 5.48 Yields given are those over all 3 steps.

Most of the fluoroalkyl ketones were commercially available. However, in the case of **248e** the precursor ketone had to be synthesised. Simple alkylation of trifluoroacetic acid using Grignard reagent gave the desired ketone (**Equation 5.10**). The conditions used were based on a literature procedure which describes the reaction of ethyl trifluoroacetate with Grignard reagent.[164] Trifluoroacetic acid, which has been used in similar reactions,[165] was employed in place of the trifluoroacetate due to reagent availability.



Equation 5.10

Initially, the racemic arylation of **248a** was carried out using phenyl boronic acid and rhodium-catalysis ($[Rh(cod)Cl]_2$). Complete conversion to desired product was observed after 30 minutes at 70 °C. The scope of the racemic reaction was then explored. Some examples are shown in **Table 5.8**. With respect to the boronic acid component, both electron rich

(**255o**) and electron poor (**255d**) aromatics worked well. The ring could also be substituted in the *ortho* (**255p**), *meta* (**255b**) and *para* (**255d** and **255o**) positions with minimal effect on the isolated product yields. The *β*-substituent of the unsaturated aldehyde could be varied from phenyl (**255a**, **b**, **d**, **g**, **o** and **p**) to fluorophenyl (**255i**), thiophenyl (**255k**) and alkyl (**255m**) groups. The fluoroalkyl group could be successfully changed from trifluoromethyl to ^{n}heptafluoropropyl (**255g**).

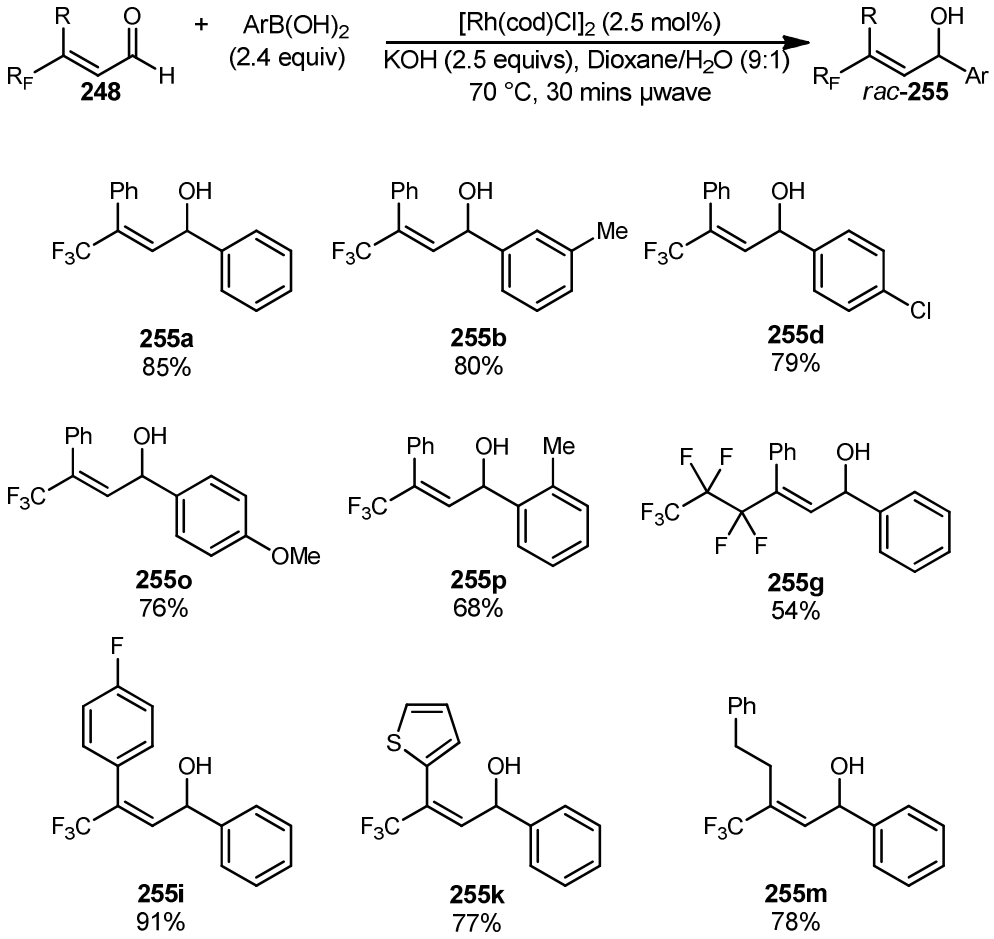
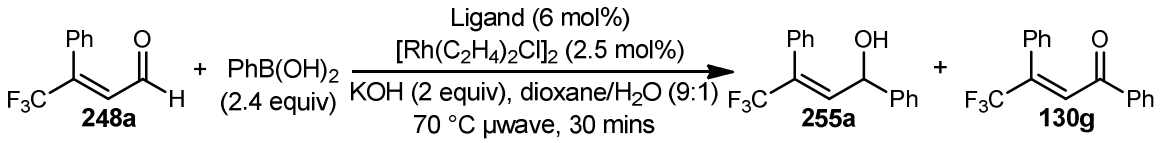
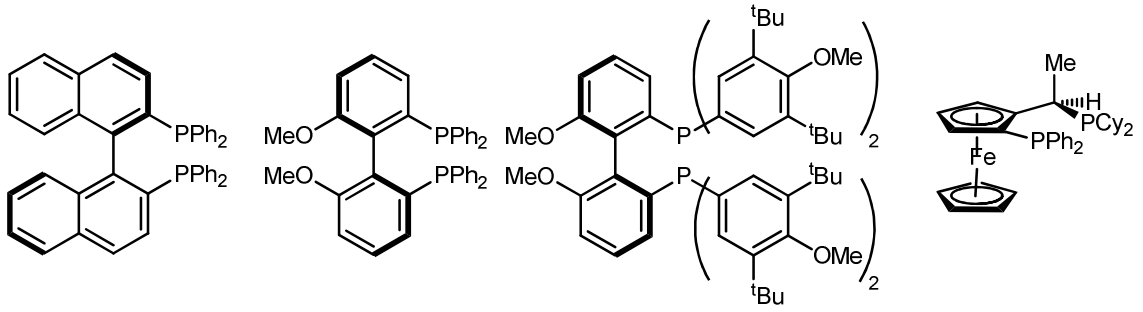


Table 5.8

Work was then carried out towards our major aim of the development of a set of enantioselective conditions to give the allylic alcohols in high enantiomeric excesses. Initial screening focused on the use of rhodium with chiral non-racemic ligands. $[Rh(C_2H_4)_2Cl]_2$ was used along with 2 equivalents of KOH in dioxane and water (9:1). Selected results of this screening are give in **Table 5.9**. A number of ligands gave good conversions to the arylation product, although many gave a substantial amount of side-product **130g**, which presumably forms by a *β*-hydride elimination of the intermediate rhodium alkoxide (**258**) instead of the desired hydrolysis (**Scheme 5.49**). Unfortunately, the best enantiomeric excess observed

during the ligand screen was 42%, which was seen with both (*R*)-MeO-BIPHEP and an alkene-sulfoxide ligand reported by Feng and co-workers.[133c)]



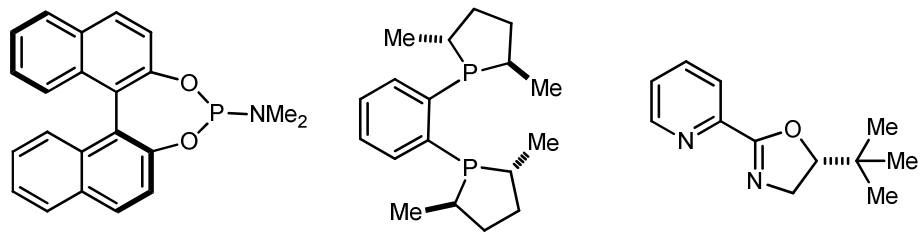


(*R*)-BINAP
78% (22%)
24% *ee* (*S*)

(*S*)-MeO-BIPHEP
>95% (<5%)
42% *ee* (*R*)

(*S*)-3,5-^{t}Bu,4-MeO-BIPHEP
69% (31%)
40% *ee* (*R*)

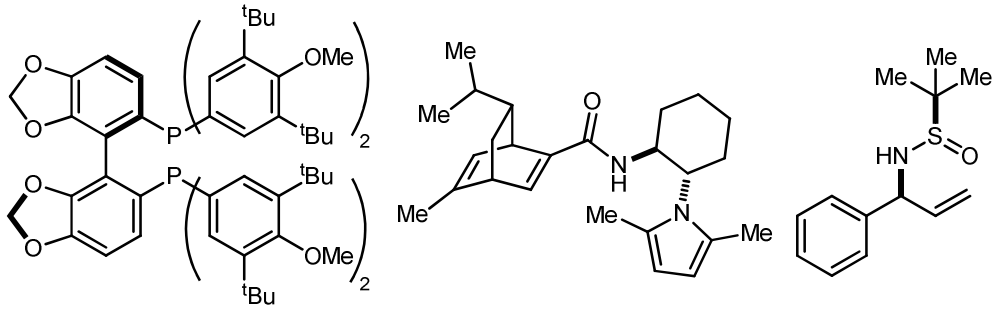
Josiphos, SL-J001-1
<5% (<5%)



(*S*)-Monophos[a]
>95% (<5%)
13% *ee* (*R*)

(*S*,*S*)-MeDuPhos
>95% (<5%)
24% *ee* (*S*)

256
62% (<5%)
36% *ee* (*S*)

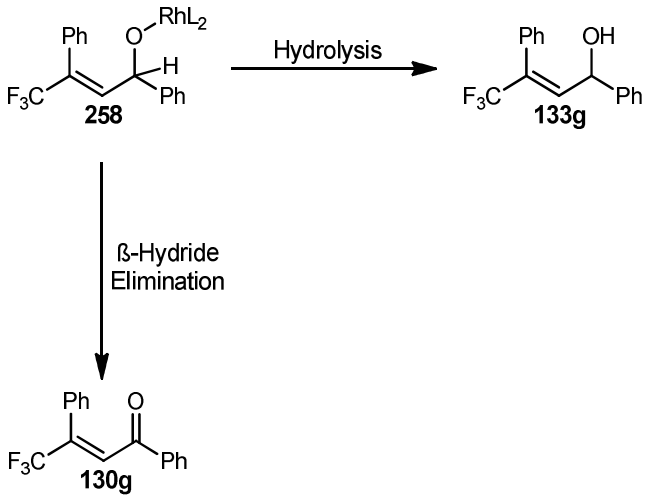


(*R*)-DTBM-SEGPHOS
>95% (<5%)
0% *ee*

189a
>95% (<5%)
4% *ee* (*S*)

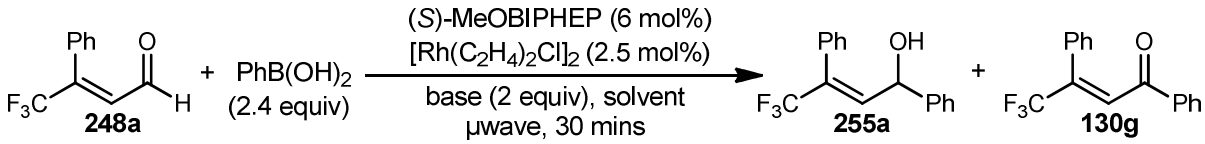
257
75% (25%)
42% *ee* (*S*)

Table 5.9 Conversions were obtained by ^{1}H and ^{19}F NMR. Values in parenthesis are the amount of **130g** formed. [a]12 mol% ligand was employed.



Scheme 5.49

Solvent, base and temperature screening gave no improvement in enantioselectivity (**Table 5.10**).



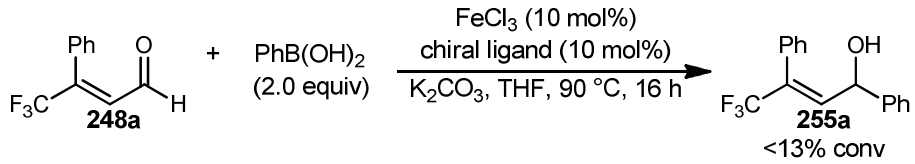
Temperature (°C)	Solvent	Base	Conversion (%)	*ee* (%)
50	Dioxane/H_2O (9:1)	KOH	<5	-
70	THF/H_2O (9:1)	KOH	<5	-
70	Toluene/H_2O (9:1)	KOH	88	16
70	Methanol	KOH	87	42
70	^{t}Butanol	KOH	73 (27)	46
70	DCM/H_2O (9:1)	KOH	79 (21)	27
70	DME/H_2O (9:1)	KOH	56	-
70	Dioxane/H_2O (9:1)	K_3PO_4	<5	-
70	Dioxane/H_2O (9:1)	NEt_3	15	33
70	Dioxane/H_2O (9:1)	K_2CO_3	>95	27

Table 5.10 Conversions were obtained by ^{1}H and ^{19}F NMR. Values in parenthesis are the amount of **130g** formed.

As rhodium was giving disappointing results, other metals (which would be more desirable anyway for cost and availability) were tried in the arylation reaction.

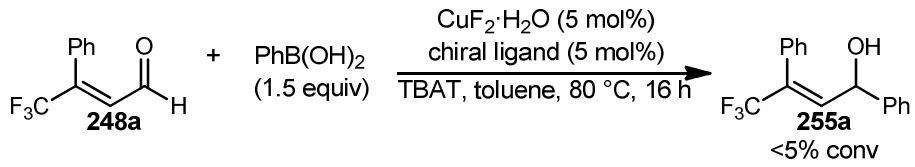
Whilst there are no examples in the literature of an enantioselective arylation of aldehydes catalysed by iron, there is a racemic report of such a reaction.[166] Only aromatic aldehydes with electron withdrawing substituents on the ring were found to undergo reaction with boronic acids under iron(III) chloride catalysis. All attempts to apply similar conditions

($FeCl_3$, K_2CO_3, THF, 90 °C) to our system employing chiral ligands gave poor results; with the highest conversion observed a disappointing 13% (**Equation 5.11**).



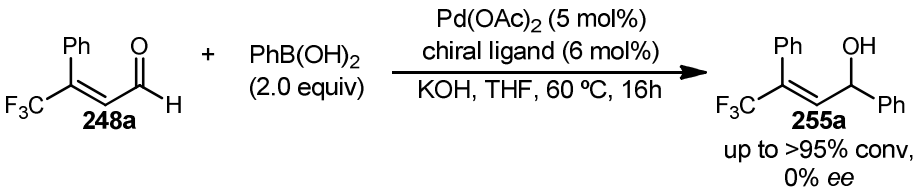
Equation 5.11

Copper catalysis was found to be even less successful; with none of the ligands (Me-DuPhos, MeO-BIPHEP, and Monophos) screened with conditions based on those reported by Shibasaki[158] ($CuF_2 \cdot H_2O$, TBAT, toluene, 100 °C), giving any product at all (**Equation 5.12**).



Equation 5.12

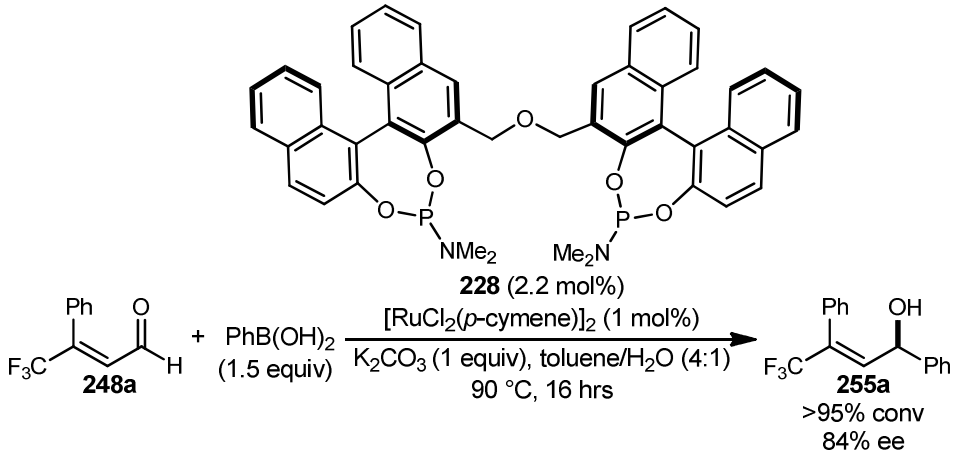
In terms of conversion, palladium was a far more suitable catalyst. With a number of ligands (including **256**, MeO-BIPHEP, and Me-DuPhos), the arylation of *β*-fluoroalkyl-*α*,*β*-unsaturated aldehydes was found to occur in high conversions at 60 °C with palladium (II) acetate and KOH (**Equation 5.13**). Unfortunately, in all cases, no enantiodiscrimination was observed.



Equation 5.13

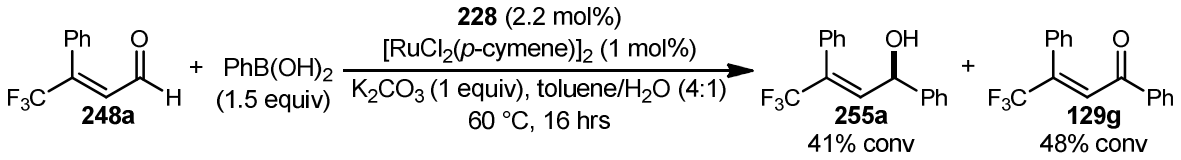
Ruthenium was another metal that showed promise from initial screening. A number of commercially-available chiral non-racemic ligands were tested in conjuction with $[RuCl_2(p\text{-cymene})]_2$ and in some cases (such as with Me-DuPhos), high conversions were observed and the reactions looked very clean by crude NMR. Unfortunately, low enantiomeric excesses

were still a problem with 22% being the highest obtained. The breakthrough was observed when Miyaura's Me-Bipam ligand[159,160,161] was synthesised and tested. Under the initial conditions attempted (**Equation 5.14**), the desired product was obtained in >95% conversion and with an enantiomeric excess of 84%.



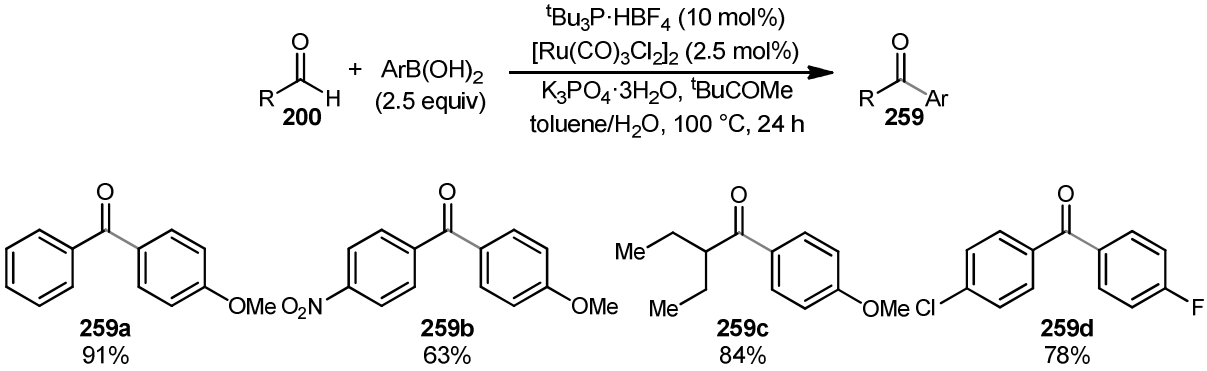
Equation 5.14

Additional screening was then carried out to determine the optimum conditions employing this ligand. As the reaction completed cleanly at 90 °C, lower temperatures were investigated first. Surprisingly, when the temperature was decreased to 60 °C, **255a** was no longer the major product obtained and 48% of the reaction mixture was found to be **129g** (11% starting material also remained after 16 hours reaction time and the remaining 41% was the desired arylation product, **Equation 5.15**).



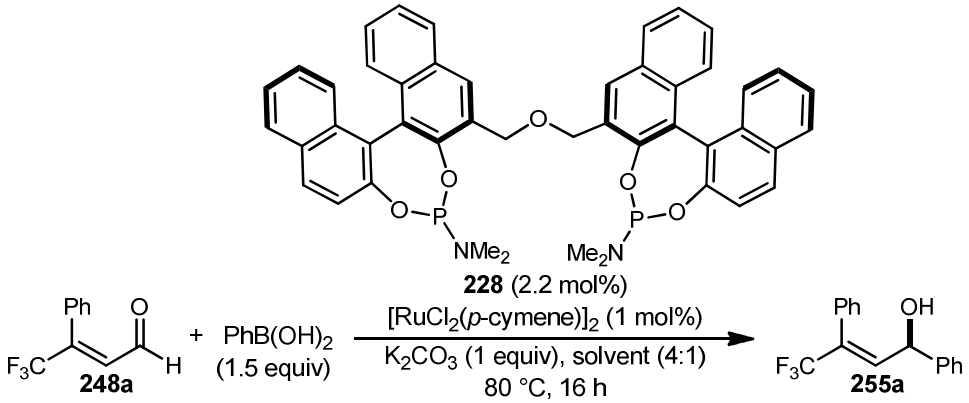
Equation 5.15

The ketone product is most likely formed by a beta-hydride elimination as in **Scheme 5.49**. There is literature precedent for ruthenium-catalysed arylation of aldehydes with boronic acids giving a ketone as the product (**Scheme 5.50**).[167]



Scheme 5.50

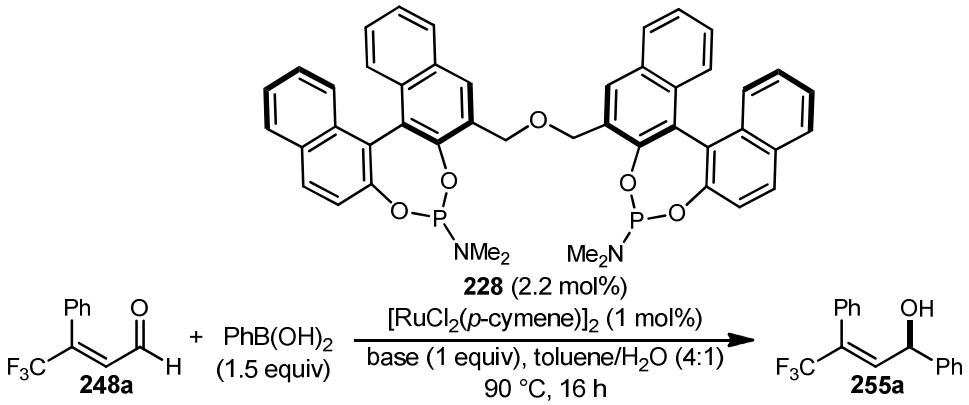
A brief survey of alternative solvents was also conducted (although choice here was restricted by the requirement for a high boiling point). No desired product was obtained when dioxane or DMF were used in a 4:1 ratio with water. Water alone also returned only starting material. Dichloroethane was found to give 86% conversion and an *ee* of 84% after 16 hours, but as there was no clear advantage to the use of DCE over toluene, no change was made to the reaction solvent (**Table 5.11**).



Solvent	Conversion (%)	Enantiomeric Excess (%)
Toluene/H_2O (4:1)	>95	84
dioxane/H_2O (4:1)	<5	-
DMF/H_2O (4:1)	<5	-
H_2O	<5	-
DCE/H_2O (4:1)	86	84

Table 5.11

The base employed was found to have a highly significant effect on the enantioselectivity of the reaction as well as the amount of conversion to product (**Table 5.12**) and, again, the initial choice of base was found to be the optimum after screening was completed.



Base	Conversion (%)	Enantiomeric Excess (%)
K_2CO_3	>95	85
KOH	80	78
NEt_3	40	16
K_3PO_4	50	0

Table 5.12

The ethyl analogue of the Bipam ligand (**264**, **Figure 5.1**) was also synthesised but was found to give much poorer *ee* values (<5% for **255a** and 20% for **255d**).

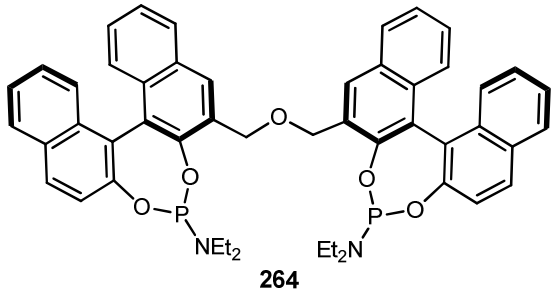
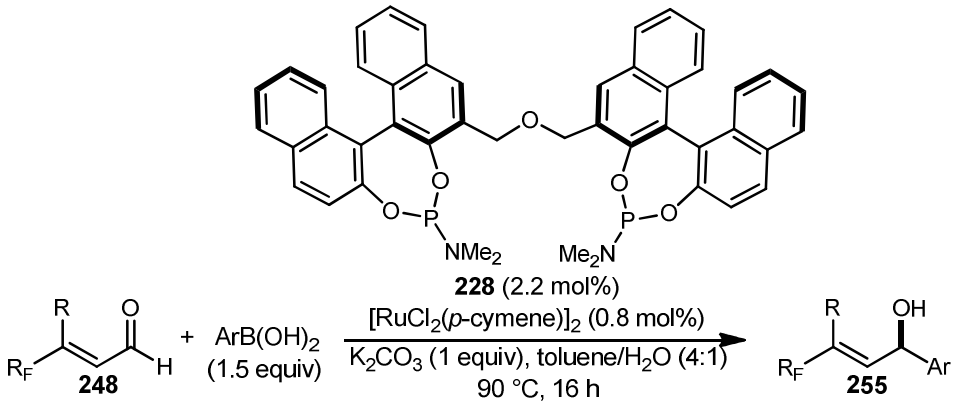


Figure 5.1

After the optimisation screening had been completed, the conditions selected were those that were initially tested (**Equation 5.9**). The scope was then examined (**Table 5.13**). In addition to phenylboronic acid (**255a**, **255g**, **255i**, **255k** and **255m**), arylboronic acids containing alkyl (**255b**, **255c**, and **255n**), halogen (**255d**, **255j** and **255l**), or methoxy substituents (**255e**) were successful reaction partners, as was 2-naphthylboronic acid (**255f** and **255h**). With respect to the *β*-substituents of the enal, variation of the phenyl group in **255a** to 4-fluorophenyl (**255i** and **255j**), and 2-thienyl (**255k** and **255l**) is well tolerated. However, with an alkyl group (**255m** and **255n**) yields were lower. This is due to some starting material remaining in the reaction mixture as well as some degradation under the reaction conditions. Furthermore, the

β-perfluoroalkyl substituent may be varied from trifluoromethyl to *n*-heptafluoropropyl (**255g** and **255h**) without affecting the efficiency of the reaction. The enantiomeric excesses of the products were fairly consistent (generally >80% *ee*), though slightly diminished selectivities were observed in some cases (**255e**, **255h**, and **255m**) and much lower values in others (**255q**, **255r**, and **255s**, *vide infra*). In addition to the arylation products, the reactions also often produced varying quantities of the carboxylic acids resulting from the oxidation of the enal. Whilst the origin of this oxidation is unknown, attempts were made to decrease the amount of this unwanted side-product generated and these are described later in the chapter.



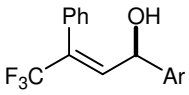
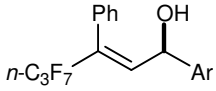
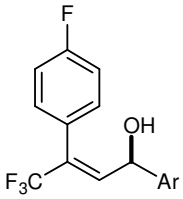
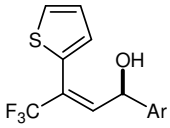
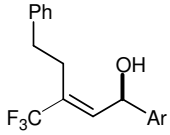
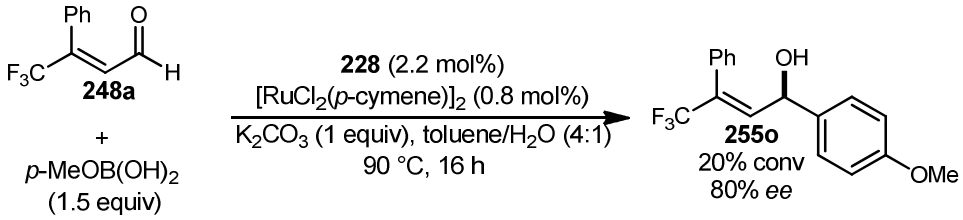
entry	product		yield (%)	*ee* (%)
1		**255a** Ar = Ph	66	84
2		**255b** Ar = 3-MeC_6H_4	64	85
3		**255c** Ar = 3,5-$Me_2C_6H_3$	62	84
4		**255d** Ar = 4-ClC_6H_4	66	87
5		**255e** Ar = 3-$MeOC_6H_4$	50	79
6		**255f** Ar = 2-naphthyl	64	85
7		**255g** Ar = Ph	66	86
8		**255h** Ar = 2-naphthyl	52	76
9		**255i** Ar = Ph	60	81
10		**255j** Ar = 4-BrC_6H_4	61	84
11		**255k** Ar = Ph	71	85
12		**255l** Ar = 4-FC_6H_4	59	87
13		**255m** Ar = Ph	40	79
14		**255n** Ar = 4-MeC_6H_4	42	85

Table 5.13 All yields are those of isolated material. All reactions were conducted on a 0.5 mmol scale

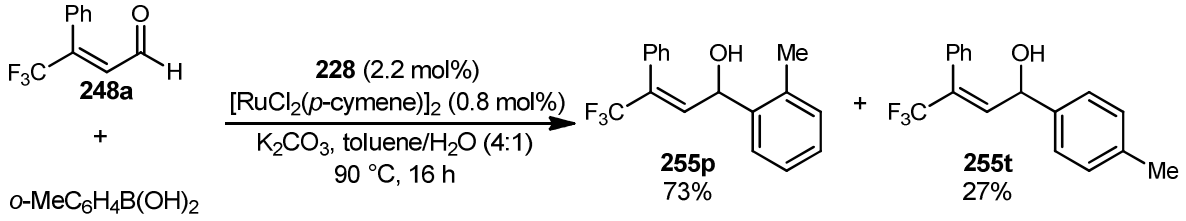
Unfortunately, not all of the arylations tested were as successful as those shown in **Table 5.12**. For example, whilst the reaction with most electron-deficient boronic acids occurred

smoothly, electron-donating substituents were less well tolerated. Reaction of *p*-methoxyphenyl boronic acid with **248a** occurred smoothly under the optimised racemic conditions to give the desired product (**255o**) in 76% yield (**Table 5.8**). Under the enantioselective ruthenium-catalysed conditions, only a 20% conversion was observed, although the enantioselectivity was still high (80% *ee*).



Equation 5.16

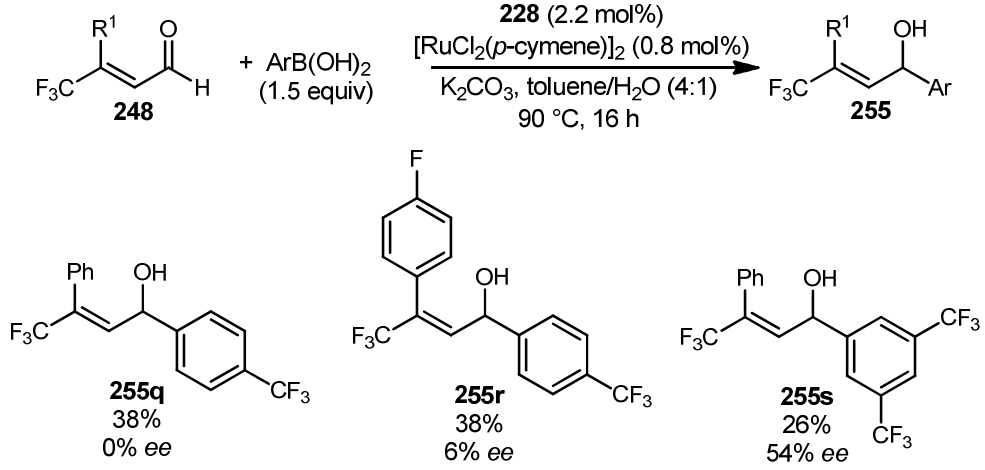
Interesting results were obtained with *ortho*-substituents present. In the reaction of **248a** with *o*-tolyl boronic acid, only 73% of the expected product **255p** was observed. The remaining 27% was found to be **255t**, the product of reaction with *p*-tolyl boronic acid (**Equation 5.17**). Again, this is a result that was not observed under the racemic rhodium-catalysed arylation conditions. The mechanism of formation of this product is as yet unclear, although it seems likely that a migration occurs at some point. Incorporation of the toluene reaction solvent through a C-H activation process has been ruled out through control experiments in which no boronic acid was added. *O*-fluorophenyl boronic acid gave less than 5% conversion to product. There are no reports of the application of *o*-substituted arylboronic acids in the ruthenium-catalysed arylation reports from the group of Miyaura.[159,160,161]



Equation 5.17

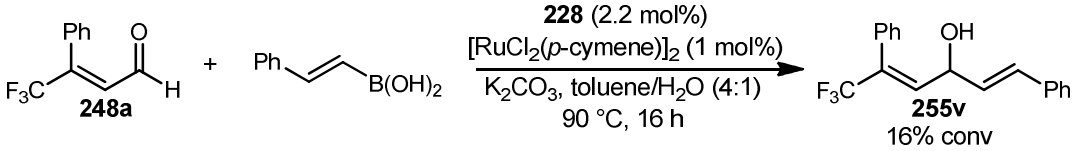
Another class of boronic acid that gave unexpected, and as yet unexplained, results were those containing trifluoromethyl substituents. The reaction with *p*-trifluoromethylphenylboronic acid gave the desired product in somewhat diminished yields (38% for both **255q** and **255r**), and the enantiomeric excesses were found to be substantially

lower (0% for **255q** and 6% for **255r**, **Scheme 5.51**). The reaction of 3,5-ditrifluoromethylphenylboronic acid was also found to give the product (**255s**) in low yield (26%, some starting material remained) and again with an *ee* lower than expected (54%, **Scheme 5.51**).



Scheme 5.51

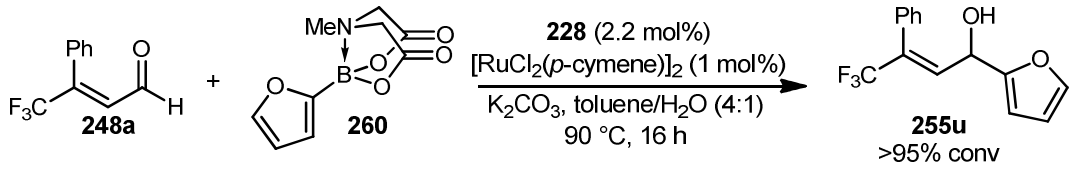
Functional groups on the boronic acid that were found to inhibit the reaction were ketones and nitriles. It is possible that this is due to the co-ordination of these groups to ruthenium preventing the transmetallation to ruthenium and/or the insertion into the aldehyde C=O bond. Alkenyl boronic acids were also tested, although these are known to be more challenging due to the rapid protodeboration of these species.[130] 16% conversion to the desired product was observed in the reaction of trans-2-phenylvinyl boronic acid with **248a**, which did not increase when the MIDA-boronate equivalent (from which the boronic acid is slowly released by hydrolysis) was used (**Equation 5.18**).



Equation 5.18

Heteroaromatic boronic acids were also found to give very poor conversion to desired product. However, MIDA-boronates were found to be much more successful here and complete conversion to desired product was observed on a 0.1 mmol scale test reaction with

2-furanyl MIDA-boronate (**Equation 5.19**). Unfortunately, upon scale-up of this reaction, the product was found to degrade rapidly upon standing as well as upon silica gel and no purification could be carried out.



Equation 5.19

As described earlier, the isolated yields for the ruthenium-catalysed arylation were found to be somewhat lower than expected given the appearance of the crude NMR, in which in almost all cases, only the product of arylation was observed. Whilst testing various work-up procedures in order to remedy this issue, a component of the reaction mixture which remained in the aqueous layer upon extraction with several organic solvents was discovered. Analysis of this compound (isolated upon reaction of **248c** with phenylboronic acid) revealed it to be carboxylic acid, **261** (**Figure 5.2**). It was believed that this was formed by oxidation of the starting material aldehyde under the reaction conditions. Inhibition of this oxidation was required to increase the yields for this arylation reaction.

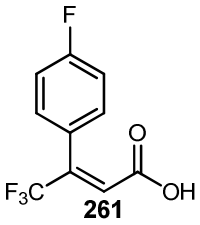


Figure 5.2

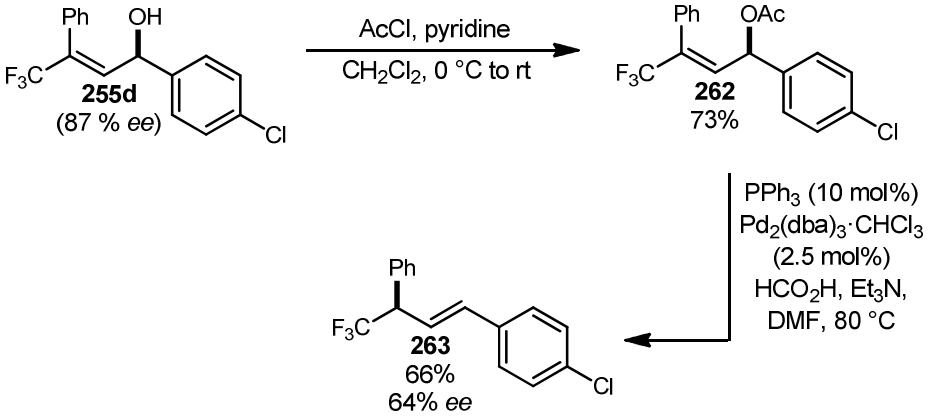
As the use of hydroquinone and TEMPO in ruthenium-catalysed oxidations of alcohols to aldehydes prevented any over-oxidation to the carboxylic acid,[168] it was reasoned that the addition of these compounds to the ruthenium-catalysed arylation reaction mixture could prevent oxidation of the aldehyde. Unfortunately, no substantial improvement was observed upon addition of various amounts of these compounds, or sodium ascorbate, as an additive. It was also considered possible that the use of water in this reaction may be encouraging the oxidation. To test this, 5 equivalents of methanol was used as a proton source in place of the water, but carboxylic acid formation was still observed. Increasing the number of equivalents

of boronic acid employed to 2.5 was also tried with no success. An explanation for and solution to the problem of carboxylic acid formation under the optimised conditions is still sought.

Once conditions had been obtained for the enantioselective arylation of β-fluoroalkyl-α,β-unsaturated aldehydes, we looked to demonstrate potential uses of the chiral allylic alcohols thus formed in further manipulations to give other useful enantioenriched fluorinated compounds.

A survey of the existing literature revealed a small number of reactions that employed β-fluoroalkyl allylic alcohols similar to **255a**-**255n**. The adaptation of one of these reactions to allow the employment of products **255a-255n** was then embarked upon.

Konno and co-workers have reported the palladium-catalysed formate reduction of fluorine-containing allylic mesylates and acetates.[57] Conversion of alcohol **255d** into the corresponding acetate ester **262** was followed by the application of the conditions for formate-reduction reported by Konno (**Equation 5.20**). This afforded **263** containing a stereogenic trifluoromethyl group in 66% yield. Unfortunately, the reaction was accompanied by a diminuation in enantiopurity upon going from **255d** (87% *ee*) to **263** (64% *ee*). This is consistent with the transformation reported by Konno on a very similar substrate.



Equation 5.20

The above transformation illustrates just one of the possible transformations that could be carried out on the arylation products to give a diverse range of enantioenriched fluorinated structures.

5.3 Conclusions and Future Work

An investigation has been conducted into the arylation of *β*-fluoroalkyl-*α*,*β*-unsaturated compounds. Under standard rhodium-catalysed arylation conditions, both enones and enals were found to undergo 1,2-arylation to give allylic alcohols as products. Both a racemic and an enantioselective arylation of enones have been developed. The conversions and enantiomeric excesses are somewhat modest for the enantioselective arylation of enones. Better results have been obtained for the enals for which a set of ruthenium-catalysed conditions affording chiral allylic alcohols in good yields and *ee*s have been discovered. The products of this reaction have also been shown to undergo furthur elaboration to give fluoroalkylated stereocentres with good enantiomeric excesses.

Work into the mechanism of the ruthenium-catalysed process could help to extend the scope of this reaction to include the addition of ortho-substituted aryl species and alkenyl groups. It may also allow conditions leading to higher isolated yields to be developed thorugh the removal of the unwanted oxidation. The reaction of esters also requires further work in order to obtain suitable conditions for the conjugate arylation of this challenging substrate class.

5.4 Experimental

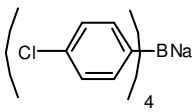
General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. THF, toluene, dichloromethane, diethyl ether and methanol were dried and purified by passage through activated alumina columns using a solvent purification system. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or vanillin as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[40] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Shimadzu IRAffinity-1 instrument as a thin film or as a solid. ^{1}H NMR spectra were recorded on a Bruker AVA500 (500 MHz) spectrometer or a Bruker AVA400 (400 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm; CD_3OD at 4.84 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), sept (septet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA500 (125.8 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm; CD_3OD at 49.05 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker AVA400 (378 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield of $CFCl_3$, using fluorobenzene as internal standard (C_6H_5F at –113.2 ppm). ^{31}P NMR spectra were recorded on a bruker AVA400 (161.9 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield of phosphoric acid. High-resolution mass spectra were recorded using electrospray ionisation (ES), electron impact ionisation (EI) or atmospheric solids analysis probe (ASAP) techniques on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer or a Thermofisher LTQ Orbitrap XL spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea or using electron impact ionisation on a Finnigan MAT 900 spectrometer at the University of Edinburgh. Optical rotations were

performed on an Optical Activity POLAAR 20 polarimeter. Chiral HPLC analysis was performed on an Agilent 1100 instrument or an Agilent 1260 instrument using 4.6 x 250 mm columns.

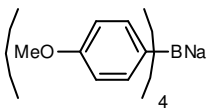
General Procedure A: Synthesis of Sodium Tetraarylborates A.

To magnesium turnings (3.24 g, 133 mmol) and a flake of iodine in Et_2O (100 mL) was added the appropriate bromobenzene (111 mmol, 5.55 equiv) in Et_2O (100 mL) over 1 hour. After 90 minutes of further stirring, $NaBF_4$ (2.20 g, 20 mmol) was added. After 40 hours of stirring at room temperature, the reaction mixture was poured into sodium carbonate solution (500 mL, 1M) and stirred for a further 15 minutes. The mixture was filtered through a celite layer, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The solid obtained was washed with $CHCl_3$ and hexane (1:1) to afford the desired sodium tetraarylborate salt.



Sodium tetrakis(4-chlorophenyl)borate (245a)[169]

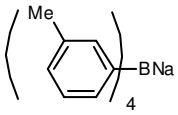
The title compound was prepared according to General Procedure A from 4-bromochlorobenzene (21.3 g, 111 mmol) to give an off-white solid (6.05 g, 73%). ^{1}H NMR (500 MHz, C_3DOD) δ 7.17-7.13 (8H, m, Ar**H**), 6.98 (8H, d, J = 8.2 Hz, Ar**H**); ^{13}C NMR (125.8 MHz, C_3DOD) δ 162.9 (4 x C, $J_{^{11}B\text{-}H}$ = 49.7 Hz, $J_{^{10}B\text{-}H}$ = 16.6 Hz), 139.1 (8 x CH), 129.9 (4 x C), 127.2 (8 x CH, $J_{^{11}B\text{-}H}$ = 5.4 Hz).



Sodium tetrakis(4-methoxyphenyl)borate (245b)[170]

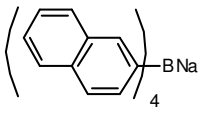
To a solution of $NaBF_4$ (2.20 g, 20 mmol) in Et_2O (100 mL) was added 4-methoxyphenyl magnesium bromide (100 mL, 1M in THF) over 5 minutes. After 40 hours of stirring at room temperature, the reaction mixture was poured into sodium carbonate solution (500 mL, 1M) and stirred for a further 15 minutes. The mixture was filtered through a celite layer, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The solid obtained was washed with $CHCl_3$ and hexane (1:1) to afford an off-white solid (3.81 g, 43%). ^{1}H NMR (500 MHz, C_3DOD) δ 7.23 (8H, br, Ar**H**), 6.65 (8H, d, J = 7.9 Hz, Ar**H**), 3.73 (12H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz,

C_3DOD) δ 158.1 (4 x C, $J_{^{11}B\text{-}H}$ = 50.0 Hz, $J_{^{10}B\text{-}H}$ = 16.6 Hz), 157.3 (4 x C), 138.5 (8 x CH), 112.9 (8 x CH, $J_{^{11}B\text{-}H}$ = 2.8 Hz), 56.3 (4 x CH_3).



Sodium tetrakis(3-methylphenyl)borate (245c)[170]

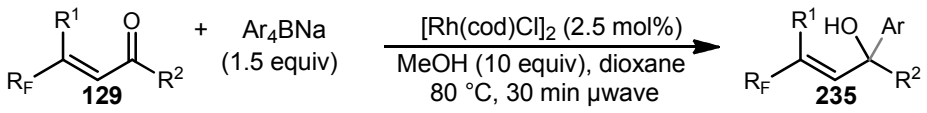
The title compound was prepared according to General Procedure A from bromotoluene (13.5 mL, 111 mmol) to give an off-white solid (3.15 g, 42%). ^{1}H NMR (500 MHz, C_3DOD) δ 7.18 (4H, br, Ar**H**), 7.11 (4H, app s, Ar**H**), 6.90 (4H, t, *J* = 7.4 Hz, Ar**H**), 6.69 (4H, d, *J* = 7.3 Hz, Ar**H**), 2.19 (12H, s, ArC**H**$_3$); ^{13}C NMR (125.8 MHz, C_3DOD) δ 166.4 (4 x C, $J_{^{11}B\text{-}H}$ = 49.4 Hz, $J_{^{10}B\text{-}H}$ = 16.5 Hz), 139.0 (4 x CH, $J_{^{11}B\text{-}H}$ = 1.4 Hz), 135.5 (4 x CH, $J_{^{11}B\text{-}H}$ = 2.8 Hz), 135.4 (4 x CH, $J_{^{11}B\text{-}H}$ = 1.1 Hz), 127.0 (4 x CH, $J_{^{11}B\text{-}H}$ = 2.9 Hz), 124.1 (4 x C), 23.0 (4 x CH_3).



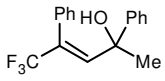
Sodium tetrakis(2-naphthyl)borate (245d)[171]

The title compound was prepared using a reported procedure.[171] One-fifth of a solution of 2-bromonaphthalene (3.40 g, 16.4 mmol) in THF (20 mL) was added to magnesium turnings (0.39 g, 16 mmol) and a flake of iodine. The mixture was heated until Grignard formation began. The remaining solution was then added slowly. After 90 minutes of stirring at room temperature, a solution of boron trifluoride diethyl etherate (1.64 mL, 13.3 mL) in THF (10 mL) was added slowly. The reaction was stirred for 45 minutes and then poured into sodium carbonate solution (40mL, 0.4 M). After 15 minutes stirring, the mixture was extracted with Et_2O (20 mL x 3) and the combined organic layers were combined, dried ($MgSO_4$) and solvent removed under reduced pressure to give an off-white solid (1.43 g, 66%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.90-7.88 (4H, m, Ar**H**), 7.76-7.73 (8H, m, Ar**H**), 7.61-7.57 (8H, m, Ar**H**), 7.29-7.25 (8H, m, Ar**H**); ^{13}C NMR (126 MHz, CD_3OD) δ 163.7 (4 x C, $J_{^{11}B\text{-}H}$ = 49.5 Hz, $J_{^{10}B\text{-}H}$ = 16.4 Hz), 138.3 (4 x CH), 135.2 (4 x C, $J_{^{11}B\text{-}H}$ = 2.9 Hz), 134.3 (4 x CH), 132.7 (4 x C), 128.5 (4 x CH), 128.1 (4 x CH), 124.7 (4 x CH), 124.7 (4 x CH, $J_{^{11}B\text{-}H}$ = 2.6 Hz), 123.8 (4 x CH).

General Procedure B: Racemic Arylation of *β*-Fluoroalkyl-*α,β*-Unsaturated Ketones

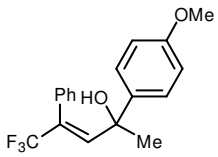


To a solution of $[Rh(cod)Cl]_2$ (6.2 mg, 0.013 mmol), the appropriate sodium tetraarylborate salt (0.75 mmol), and the appropriate *α,β*-unsaturated ketone (0.50 mmol) in 1,4-dioxane (1.8 mL) was added MeOH (0.2 mL). The reaction mixture was then heated under microwave irradiation at 80 °C for 30 minutes. The mixture was filtered through a short plug of SiO_2 eluting with $CHCl_3$ and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired alcohol.



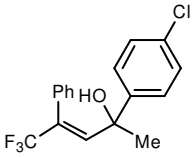
(3*E*)-5,5,5-trifluoro-2,4-diphenylpent-3-en-2-ol (235a)

The title compound was prepared according to General Procedure B from **129a** (107 mg, 0.50 mmol) and sodium tetraphenylborate (257 mg, 0.75 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a pale yellow oil (72 mg, 49%). R_f = 0.37 (20% EtOAc/hexane); IR (film) 3435 (OH), 1283, 1227, 1173, 1117, 1072, 766, 756, 698, 579 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.36 (8H, m, Ar**H**), 7.09 (2H, d, *J* = 7.2 Hz, Ar**H**), 6.85 (1H, q, *J* = 1.5 Hz, **=CH**), 1.80 (1H, s, O**H**), 1.61 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 146.7 (C), 141.6 (CH, q, *J* = 5.2 Hz), 131.4 (C), 129.8 (2 x CH), 129.8 (C, q, *J* = 29.7 Hz), 128.8 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 124.8 (2 x CH), 123.2 (C, q, *J* = 273.8 Hz), 74.4 (C), 31.1 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.0 (3F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{15}F_3O$ [M^+]: 292.1070, found: 292.1067.



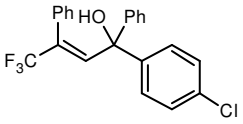
(3*E*)-5,5,5-trifluoro-2-(4-methoxyphenyl)-4-phenylpent-3-en-2-ol (235b)

The title compound was prepared according to General Procedure B from **129a** (107 mg, 0.50 mmol) and **245b** (330 mg, 0.75 mmol) and purified by column chromatography (2→10% EtOAc/hexane) to give a pale yellow oil (93 mg, 58%). IR (film) 3420 (OH), 1510, 1283, 1250, 1231, 1173, 1115, 1030, 831, 702 cm^{-1}; R_f = 0.28 (20% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.37 (3H, m, Ar**H**), 7.24 (2H, dt, *J* = 9.0, 2.8 Hz, Ar**H**), 7.11 (2H, d, *J* = 7.1 Hz, Ar**H**), 6.85 (2H, dt, *J* = 9.0, 2.5 Hz, Ar**H**), 6.83 (1H, q, *J* = 1.5 Hz, =C**H**), 3.82 (3H, s, OC**H**$_3$), 1.74 (1H, s, O**H**), 1.59 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 158.8 (C), 141.8 (CH, q, *J* = 5.1 Hz), 138.9 (C), 131.5 (C), 129.8 (2 x CH), 129.5 (C, q, *J* = 29.7 Hz), 128.8 (CH), 128.3 (2 x CH), 126.2 (2 x CH), 123.2 (C, q, *J* = 273.8 Hz), 113.7 (2 x CH), 74.1 (C), 55.3 (CH_3), 30.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.9 (3F, s); HRMS (EI) Exact mass calcd for $C_{18}H_{17}F_3O_2$ [M^+]: 322.1175, found: 322.1174.



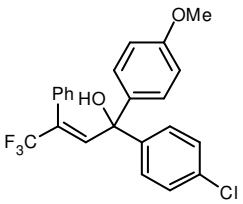
(3*E*)-2-(4-chlorophenyl)-5,5,5-trifluoro-4-phenylpent-3-en-2-ol (235c)

The title compound was prepared according to General Procedure B from **129a** (107 mg, 0.50 mmol) and **245a** (360 mg, 0.75 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a pale yellow oil (36 mg, 22%). R_f = 0.32 (20% EtOAc/hexane); IR (film) 3393 (OH), 1287, 1236, 1215, 1173, 1117, 1094, 829, 702, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22-7.37 (7H, m, Ar**H**), 7.06 (2H, d, *J* = 7.3 Hz, Ar**H**), 6.81 (1H, q, *J* = 1.5 Hz, =C**H**), 1.85 (1H, s, O**H**), 1.59 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.2 (C), 141.1 (CH, q, *J* = 5.1 Hz), 133.2 (C), 131.1 (C), 130.4 (C, q, *J* = 30.0 Hz), 129.7 (2 x CH), 128.9 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 126.4 (2 x CH), 122.8 (C, q, *J* = 274.4 Hz), 73.9 (C), 31.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.1 (3F, s); HRMS (CI) Exact mass calcd for $C_{17}H_{18}F_3NOCl$ $[M+NH_4]^+$: 344.1024, found: 344.1026.



(3*E*)-1-(4-Chlorophenyl)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-ol (235d)

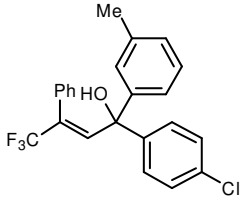
The title compound was prepared according to General Procedure B from **129e** (158 mg, 0.50 mmol) and sodium tetraphenylborate (257 mg, 0.75 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a pale yellow oil (113 mg, 58%). R_f = 0.43 (20% EtOAc/hexane); IR (film) 3570 (OH), 1285, 1273, 1229, 1173, 1123, 1094, 775, 698, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.37 (12H, m, Ar**H**), 7.16 (2H, d, *J* = 6.9 Hz, Ar**H**), 7.07 (1H, q, *J* = 1.5 Hz, **=**C**H**), 2.07 (1H, s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.6 (C), 144.4 (C), 139.9 (CH, q, *J* = 5.2 Hz), 133.5 (C), 131.4 (C), 130.5 (C, q, *J* = 29.8 Hz), 129.5 (2 x CH), 129.0 (CH), 128.58 (2 x CH), 128.56 (2 x CH), 128.5 (2 x CH), 127.90 (2 x CH), 127.89 (CH), 124.4 (2 x CH), 123.1 (C, q, *J* = 274.7 Hz), 78.6 (C); ^{19}F NMR (250 MHz, $CDCl_3$) δ –66.7 (3F, s); HRMS (ES) Exact mass calcd for $C_{22}H_{15}ClF_3O$ $[M-H]^+$: 387.0769, found: 387.0766.



(2*E*)-1-(4-Chlorophenyl)-4,4,4-trifluoro-1-(4-methoxyphenyl)-3-phenylbut-2-en-1-ol (235e)

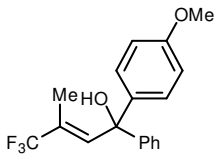
The title compound was prepared according to General Procedure B from **129e** (158 mg, 0.50 mmol) and **245b** (330 mg, 0.75 mmol) and purified by column chromatography (2→5% EtOAc/hexane) to give a yellow oil (154 mg, 74%). R_f = 0.24 (20% EtOAc/hexane); IR (film) 3392 (OH), 1510, 1282, 1250, 1175, 1121,

1092, 827, 700, 588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.39 (3H, m, Ar**H**), 7.27-7.30 (2H, m, Ar**H**), 7.20-7.26 (4H, m, Ar**H**), 7.17-7.18 (2H, m, Ar**H**), 7.03 (1H, q, *J* = 1.5 Hz, =C**H**), 6.85-6.88 (2H, m, Ar**H**), 3.82 (3H, s, OC**H**$_3$), 2.01 (1H, s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.1 (C), 144.6 (C), 140.1 (CH, q, *J* = 5.1 Hz), 137.9 (C), 133.4 (C), 131.5 (C), 130.1 (C, q, *J* = 29.9 Hz), 129.5 (2 x CH), 129.0 (CH), 128.52 (2 x CH), 128.46 (2 x CH), 127.8 (2 x CH), 127.7 (2 x CH), 123.2 (C, q, *J* = 274.7 Hz), 113.9 (2 x CH), 78.4 (C), 55.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{23}H_{17}F_3O_2Cl$ $[M-H]^+$: 417.0864, found: 417.0864.



(2*E*)-1-(4-chlorophenyl)-4,4,4-trifluoro-1-(3-methylphenyl)-3-phenylbut-2-en-1-ol (235f)

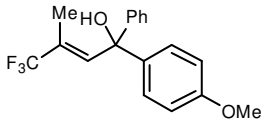
The title compound was prepared according to General Procedure B from **129e** (158 mg, 0.50 mmol) and **245c** (282 mg, 0.75 mmol) and purified by column chromatography (2% EtOAc/hexane) to give a yellow oil (96 mg, 48%). R_f = 0.53 (20% EtOAc/hexane); IR (film) 3572 (OH), 1283, 1271, 1173, 1123, 1092, 1015, 835, 785, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21-7.37 (8H, m, Ar**H**), 7.16 (2H, app d, *J* = 7.1 Hz, Ar**H**), 7.09-7.11 (3H, m, Ar**H**), 7.06 (1H, q, *J* = 1.5 Hz, =C**H**), 2.33 (3H, s, ArC**H**$_3$), 2.05 (1H, s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.6 (C), 144.5 (C), 140.0 (CH, q, *J* = 5.1 Hz), 138.3 (C), 133.5 (C), 131.4 (C), 130.3 (C, q, *J* = 29.8 Hz), 129.5 (2 x CH), 129.0 (CH), 128.7 (CH), 128.51 (2 x CH), 128.49 (2 x CH), 128.4 (CH), 127.9 (2 x CH), 127.0 (CH), 123.4 (CH), 123.2 (C, q, *J* = 286.9 Hz), 78.6 (C), 21.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.7 (3F, s); HRMS (ES) Exact mass calcd for $C_{23}H_{17}F_3OCl$ $[M-H]^+$: 401.0926, found: 401.0917.



(2*E*)-4,4,4-trifluoro-1-(4-methoxyphenyl)-3-methyl-1-phenylbut-2-en-1-ol (235g)

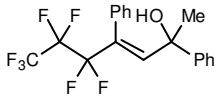
The title compound was prepared according to General Procedure B from **129b** (107 mg, 0.50 mmol) and **245b** (330 mg, 0.75 mmol) and purified by column chromatography (2→10% EtOAc/hexane) to give a yellow oil (88 mg, 53%). R_f = 0.34 (20% EtOAc/hexane); IR (film) 3363 (OH), 1510, 1298, 1248, 1175, 1111, 1032, 1015, 831, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.39 (7H, m, Ar**H**), 6.85-6.88 (2H, m, Ar**H**), 6.75 (1H, qq, *J* = 1.5, 1.4 Hz, =C**H**), 3.80 (1H, s, OC**H**$_3$), 2.39 (1H, s, O**H**), 1.80 (3H, d, *J* = 1.4 Hz, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.0 (C), 146.1 (C), 138.1 (C), 137.8 (CH, q,

J = 5.9 Hz), 128.6 (C, q, *J* = 28.8 Hz), 128.4 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 126.2 (2 x CH), 123.2 (C, q, *J* = 274.0 Hz), 113.8 (2 x CH), 78.2 (C), 55.3 (CH_3), 11.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.8 (3F, s); HRMS (EI) Exact mass calcd for $C_{18}H_{17}F_3O_2$ [M^+]: 322.1175, found: 322.1173.



(2*E*)-4,4,4-trifluoro-1-(4-methoxyphenyl)-3-methyl-1-phenylbut-2-en-1-ol (235g)

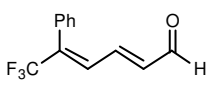
The title compound was also prepared according to General Procedure B from **129d** (107 mg, 0.50 mmol) and sodium tetraphenylborate (257 mg, 0.75 mmol), and purified by column chromatography (2% EtOAc/hexane) to give a yellow oil (30 mg, 19%). Spectral data was consistent with that above.



(3*E*)-5,5,6,6,7,7,7-heptafluoro-2,4-diphenylhept-3-en-2-ol (235h)

The title compound was prepared according to General Procedure B from **129f** (157 mg, 0.50 mmol) and sodium tetraphenylborate (257 mg, 0.75 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a yellow oil (107 mg, 55%). R_f = 0.41 (20% EtOAc/hexane); IR (film) 3379 (OH), 1229, 1209, 1179, 1111, 1099, 984, 768, 723, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.34 (8H, m, Ar**H**), 7.03 (2H, d, *J* = 7.3 Hz, Ar**H**), 6.88 (1H, s, =C**H**), 1.78 (1H, s, O**H**), 1.61 (3H, s, CC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 147.0 (C), 145.7 (CH, t, *J* = 8.0 Hz), 131.3 (C), 130.2 (2 x CH), 129.3 (C, t, *J* = 21.5 Hz), 128.8 (CH), 128.4 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 124.8 (2 x CH), 117.9 (C, qt, *J* = 288.5, 34.4 Hz), 114.1 (C, tt, *J* = 256.7, 31.3 Hz), 109.3 (C, tqt, *J* = 265.7, 34.4, 31.3 Hz), 74.7 (C), 31.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, *J* = 10.6 Hz), –(110.0-110.2) (2F, m), –(124.1-124.2) (2F, m); HRMS (CI) Exact mass calcd for $C_{19}H_{19}F_7NO$ [$M+NH_4$]$^+$: 410.1349, found: 410.1352.

Preparation of Substrates for Ruthenium-Catalysed Arylation of *β*-Perfluoroalkyl-*α*,*β*-Unsaturated Aldehydes

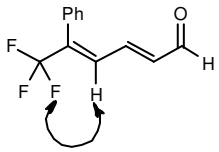


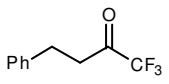
(2*E*, 4*E*)-6,6,6-trifluoro-5-phenylhexa-2,4-dienal (249)

Trifluoroacetophenone (1.6 mL, 10 mmol) was added in one portion to a solution of (formylmethylene)triphenylphosphorane (3.35 g, 11 mmol) in THF (0.2 M solution) and the resulting mixture was heated under reflux until complete consumption of

the ketone as observed by TLC analysis. The reaction was concentrated *in vacuo* and the residue was triturated thoroughly with hexane. After removal of the hexane *in vacuo*, purification of the residue by column chromatography (5% EtOAc/hexane) gave **249** as a yellow oil (361 mg, 18%) and the title compound as a yellow oil (297 mg, 13%). R_f = 0.38 (20% EtOAc/hexane); IR (solid) 1688 (C=O), 1296, 1221, 1188, 1175, 1117, 1094, 978, 775, 706 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.52 (1H, d, *J* = 7.7 Hz, **H**C=O), 7.48-7.51 (3H, m, Ar**H**), 7.32-7.34 (2H, m, Ar**H**), 6.98-7.09 (2H, m, =C**H**), 6.42 (1H, dd, *J* = 15.1, 7.5 Hz, =C**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9 (C), 144.5 (CH), 139.0 (C, q, *J* = 30.4 Hz), 136.9 (CH), 130.7 (C), 130.2 (CH, q, *J* = 5.9 Hz), 129.7 (CH), 129.6 (2 x CH), 128.8 (2 x CH), 122.8 (C, q, *J* = 273.7 Hz);^{19}F NMR (376 MHz, $CDCl_3$) δ –66.0; HRMS (CI) Exact mass calcd for $C_{12}H_{10}F_3O$ $[M+H]^+$: 227.0678, found: 227.0682.

Determination of the fluorinated alkene stereochemistry was achieved using a ^1H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E*-isomer:

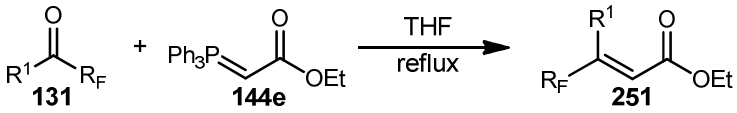




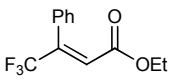
1,1,1-Trifluoro-4-phenylbutan-2-one (254)[164]

The title compound was prepared using an adapted literature procedure. 2-Phenylethylmagnesium bromide was prepared from 2-bromoethylbenzene (20.5 mL, 150 mmol) and magnesium (3.65 g, 159 mmol) in Et_2O (60 mL). At 0 °C, a solution of trifluoroacetic acid (3.8 mL, 50 mmol) in Et_2O (10 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction was then cooled again to 0 °C before 2M HCl (50 mL) was added. The mixture was extracted with Et_2O (x 3) and the combined layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by distillation under reduced pressure (84-86 °C at 15 mbar) to give the ketone as a colourless oil (7.33 g, 73%). Spectral data was consistent with that reported previously.[164] R_f = 0.19 (20% EtOAc/hexane); ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.29 (2H, m, Ar**H**), 7.26-7.19 (3H, m, Ar**H**), 3.08-3.04 (2H, m, C$\mathbf{H}_2$), 3.01-2.97 (2H, m, C$\mathbf{H}_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 190.6 (C, q, *J* = 35.3 Hz), 139.2 (C), 128.7 (2 x CH), 128.2 (2 x CH), 126.7 (CH), 115.5 (C, q, *J* = 291.9 Hz), 38.1 (CH_2), 28.3 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –79.4 (3F, s).

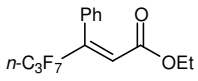
General Procedure C: Wittig Reaction of Perfluoroalkyl Ketones



The appropriate perfluoroalkyl ketone (1.0 equiv) was added in one portion to a solution of ethyl (triphenylphosphoranylidene) acetate (1.1 equiv) in THF (0.2 M solution) and the resulting mixture was heated under reflux until complete consumption of the ketone as observed by TLC analysis, or until no further reaction progress could be seen. The reaction was concentrated *in vacuo* and the residue was triturated thoroughly with hexane. After removal of the hexane *in vacuo*, purification of the residue by column chromatography gave the *α*,*β*-unsaturated ethyl ester.



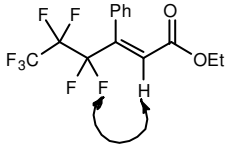
Ethyl (*E*)-4,4,4-trifluoro-3-phenyl-but-2-enoate (251a).[101c)] The title compound was prepared according to General Procedure C from ethyl (triphenylphosphoranylidene) acetate (11.5 g, 33.0 mmol) and trifluoroacetophenone (4.2 mL, 30 mmol) for 6.5 h and purified by column chromatography (20% CH_2Cl_2/hexane) to give the major *E*-isomer (the unpurified mixture contained a 9:1 *E*:*Z* ratio of isomers) as a colourless oil (6.06 g, 83%). R_f = 0.57 (20% EtOAc/hexane); IR (film) 1728 (C=O), 1229, 1209, 1182, 1134, 1115, 1101, 993, 746, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.39 (3H, m, Ar**H**), 7.31-7.29 (2H, m, Ar**H**), 6.62 (1H, q, *J* = 1.3 Hz, =C**H**), 4.05 (2H, q, *J* = 7.1 Hz, C$\mathbf{H}_2$), 1.07 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.1 (C), 142.3 (C, q, *J* = 30.9 Hz), 131.0 (C), 129.3 (CH), 128.6 (2 x CH), 128.2 (2 x CH), 124.5 (CH, q, *J* = 5.5 Hz), 122.5 (C, q, *J* = 274.8 Hz), 61.1 (CH_2), 13.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{11}F_3O_2$ [M^+]: 244.0706, found: 244.0706.

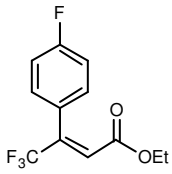


Ethyl (*E*)-4,4,5,5,6,6,6-heptafluoro-3-phenyl-hex-2-enoate (251b). The title compound was prepared according to General Procedure C from ethyl (triphenylphosphoranylidene) acetate (11.50 g, 33 mmol) and heptafluoropropyl phenyl ketone (5.6 mL, 30 mmol) for 2 h and purified by column chromatography (10% CH_2Cl_2/hexane) to give the major *E*-isomer (the unpurified mixture contained a 10:1 *E*:*Z* ratio of isomers) as a colourless oil (7.94 g, 77%). R_f = 0.58 (20% EtOAc/hexane); IR (film) 1732 (C=O), 1340, 1282, 1230, 1182, 1115, 1028, 993, 746, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.38 (3H, m, Ar**H**), 7.27 (2H, d, *J* = 7.1 Hz, Ar**H**), 6.63 (1H, t, *J* = 1.3 Hz,

=C**H**), 4.03 (2H, q, *J* = 7.1 Hz, C**H**$_2$), 1.04 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.9 (C), 141.8 (C, t, *J* = 21.6 Hz), 131.3 (C), 129.2 (CH), 129.0 (2 x CH), 128.1 (CH, t, *J* = 8.7 Hz), 128.0 (2 x CH), 117.7 (C, qt, *J* = 289.8, 35.0 Hz), 113.9 (C, tt, *J* = 257.6, 31.3 Hz), 109.0 (C, tq, *J* = 266.5, 38.2 Hz), 61.1 (CH_2), 13.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, *J* = 10.2 Hz), –112.0 (2F, q, *J* = 10.2 Hz), –124.2 (2F, br s); HRMS (CI) Exact mass calcd for $C_{14}H_{12}F_7O_2$ $[M + H]^+$: 345.0720, found: 345.0725.

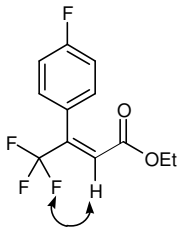
Determination of the alkene stereochemistry was achieved using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E*-isomer:

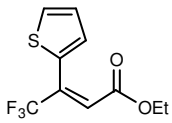




Ethyl (*E*)-4,4,4-trifluoro-3-(4-fluorophenyl)but-2-enoate (251c). The title compound was prepared according to General Procedure C from ethyl (triphenylphosphoranylidene) acetate (11.5 g, 33.0 mmol) and 2,2,2,4'-tetrafluoroacetophenone (5.76 g, 30.0 mmol) for 16 h and purified by column chromatography (1% EtOAc/hexane) to give the major *E*-isomer (the unpurified mixture contained a 10:1 *E*:*Z* ratio of isomers) as a colourless oil (5.37 g, 68%). R_f = 0.33 (20% EtOAc/hexane); IR (film) 1732 (C=O), 1607, 1512, 1285, 1258, 1231, 1171, 1159, 1126, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (2H, m, Ar**H**), 7.12-7.08 (2H, m, Ar**H**), 6.62 (1H, q, *J* = 1.5 Hz, =C**H**), 4.07 (2H, q, *J* = 7.1 Hz, C**H**$_2$), 1.11 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.9 (C), 163.3 (C, d, *J* = 249.4 Hz), 141.4 (C, q, *J* = 31.1 Hz), 130.7 (2 x CH, d, *J* = 8.5 Hz), 126.8 (C, d, *J* = 3.5 Hz), 124.9 (CH, q, *J* = 5.4 Hz), 122.4 (C, q, *J* = 274.6 Hz), 115.4 (2 x CH, d, *J* = 21.9 Hz), 61.2 (CH_2), 13.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.8 (3F, s), –111.6 (1F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{10}F_4O_2$ $[M^+]$: 262.0611, found: 262.0615.

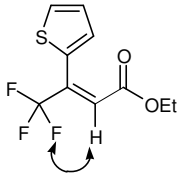
Determination of the alkene stereochemistry was achieved using a ^{1}H–^{19}F HOESY experiment which showed the following diagnostic peak for the *E*-isomer:

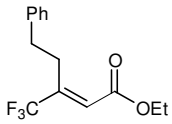




Ethyl (*Z*)-4,4,4-trifluoro-3-(thiophen-2-yl)but-2-enoate (251d). The title compound was prepared according to General Procedure C from ethyl (triphenylphosphoranylidene) acetate (13.41 g, 38.5 mmol) and trifluoroacetylthiophene (4.5 mL, 35 mmol) for 16 h and purified by column chromatography (1% acetone/hexane) to give the major *Z*-isomer (the unpurified mixture contained a 8:1 *Z*:*E* ratio of isomers) as a colourless oil (4.97 g, 57%). R_f = 0.54 (20% EtOAc/hexane); IR (film) 1730 (C=O), 1433, 1281, 1258, 1231, 1180, 1132, 1026, 853, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 7.26 (1H, app d, *J* = 3.6 Hz, Ar**H**), 7.08 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 6.61 (1H, q, *J* = 1.3 Hz, =C**H**), 4.18 (2H, q, *J* = 7.1 Hz, C$\mathbf{H}_2$), 1.20 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.3 (C), 134.2 (C, q, *J* = 31.9 Hz), 130.3 (CH), 130.0 (C), 128.7 (CH), 127.0 (CH), 124.5 (CH, q, *J* = 5.4 Hz), 122.1 (C, q, *J* = 275.3 Hz), 61.4 (CH_2), 13.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.4 (3F, s); HRMS (EI) Exact mass calcd for $C_{10}H_9F_3O_2S$ [M^+]: 250.0270, found: 250.0268.

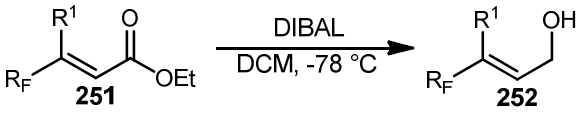
Determination of the alkene stereochemistry was achieved using a ^1H–^{19}F HOESY experiment which showed the following diagnostic peak for the *Z*-isomer:



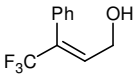


Ethyl (*E*)-5-phenyl-3-(trifluoromethyl)pent-2-enoate (251e).[101c)] The title compound was prepared according to General Procedure C from ethyl (triphenylphosphoranylidene) acetate (5.37 g, 15.4 mmol) and **254** (2.83 g, 14.0 mmol) for 2 h and purified by column chromatography (10% CH_2Cl_2/hexane) to give the major *E*-isomer (the unpurified mixture contained a 14:1 *E*:*Z* ratio of isomers) as a colourless oil (2.65 g, 70%). R_f = 0.67 (20% EtOAc/hexane); IR (film) 1726 (C=O), 1312, 1296, 1271, 1207, 1165, 1126, 1030, 895, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (4H, m, Ar**H**), 7.24-7.20 (1H, m, Ar**H**), 6.38 (1H, q, *J* = 1.0 Hz, =C**H**), 4.23 (2H, q, *J* = 7.1 Hz, C$\mathbf{H}_2$CH$_3$), 2.99-2.95 (2H, m, C$\mathbf{H}_2$CH$_2$), 2.88-2.84 (2H, m, CH$_2$C$\mathbf{H}_2$), 1.32 (3H, t, *J* = 7.1 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.4 (C), 145.2 (C, q, *J* = 29.1 Hz), 140.7 (C), 128.5 (2 x CH), 128.4 (2 x CH), 126.3 (CH), 123.5 (C, q, *J* = 275.2 Hz), 122.7 (CH, q, *J* = 6.0 Hz), 61.0 (CH_2), 35.0 (CH_2), 29.0 (CH_2), 14.1 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.1 (3F, s); HRMS (EI) Exact mass calcd for $C_{14}H_{15}F_3O_2$ [M^+]: 272.1019, found: 272.1022.

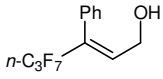
General Procedure D: DIBAL Reduction of *β*-Perfluoroalkyl-*α*,*β*-Unsaturated Ethyl Esters



To a solution of the appropriate ester (1.0 equiv) in CH_2Cl_2 (0.4 M) at –78 °C was added DIBAL (1.0 M in hexane, 2.4 equiv) over 5 min. After stirring at –78 °C for 1.5 h, the mixture was allowed to warm to 0 °C over 1 h. After a further 30 min, the reaction was quenched carefully with 2.0 M HCl solution. The aqueous layer was separated and extracted with CH_2Cl_2 (2 x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the allylic alcohol.

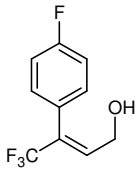


(*E*)-4,4,4-Trifluoro-3-phenylbut-2-en-1-ol (252a).[101c] The title compound was prepared according to General Procedure D from ester **251a** (7.77 g, 31.8 mmol) and purified by column chromatography (20% EtOAc/hexane) to give a colourless oil (4.37 g, 68%). R_f = 0.19 (20% EtOAc/hexane); IR (film) 3327 (OH), 1292, 1169, 1117, 1042, 1026, 907, 772, 702, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.40 (3H, m, Ar**H**), 7.26-7.24 (2H, m, Ar**H**), 6.57 (1H, tq, *J* = 6.3, 1.5 Hz, =C**H**), 4.16-4.15 (2H, m, C$\mathbf{H}_2$), 1.73 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 134.7 (CH, q, *J* = 5.4 Hz), 132.4 (C, q, *J* = 30.2 Hz), 131.3 (C), 129.3 (2 x CH), 128.9 (CH), 128.5 (2 x CH), 123.0 (C, q, *J* = 273.3 Hz), 59.2 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.2 (3F, s); HRMS (EI) Exact mass calcd for $C_{10}H_9F_3O$ [M^+]: 202.0600, found: 202.0598.

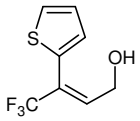


(*E*)-4,4,5,5,6,6,6-Heptafluoro-3-phenylhex-2-en-1-ol (252b). The title compound was prepared according to General Procedure D from ester **251b** (3.00 g, 8.72 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil (2.29 g, 87%). R_f = 0.35 (20% EtOAc/hexane); IR (film) 3341 (OH), 1227, 1198, 1180, 1138, 1113, 1028, 745, 712, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.38 (3H, m, Ar**H**), 7.22-7.20 (2H, m, Ar**H**), 6.57 (1H, tt, *J* = 6.1, 1.4 Hz, =C**H**), 4.13-4.11 (2H, m, C$\mathbf{H}_2$), 1.91 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.6 (CH, t, *J* = 8.3 Hz), 131.6 (C), 131.5 (C, t, *J* = 21.7 Hz), 129.7 (2 x CH), 128.9 (CH), 128.4 (2 x CH), 117.9 (C, qt, *J* = 288.3, 34.4 Hz), 114.1 (C, tt, *J* = 256.2, 31.0 Hz), 109.1 (C, tq, *J* = 265.6, 37.8 Hz),

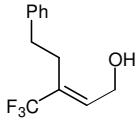
59.5 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, *J* = 10.3 Hz), –111.0 (2F, q, *J* = 10.3 Hz), –124.5 (2F, s); HRMS (ESI) Exact mass calcd for $C_{12}H_{13}F_7ON$ $[M+NH_4]^+$: 320.0880, found: 320.0880.



(*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)but-2-en-1-ol (252c). The title compound was prepared according to General Procedure D from ester **251c** (5.20 g, 19.8 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil (3.40 g, 78%). R_f = 0.22 (20% EtOAc/hexane); IR (film) 3319 (OH), 1512, 1294, 1229, 1171, 1119, 1098, 1032, 839, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.21 (2H, m, Ar**H**), 7.12-7.07 (2H, m, Ar**H**), 6.56 (1H, tq, *J* = 6.2, 1.5 Hz, =C**H**), 4.38 (2H, dq, *J* = 6.2, 2.5 Hz, C$\mathbf{H}_2$), 1.70 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.0 (C, d, *J* = 248.9 Hz), 135.1 (CH, q, *J* = 5.3 Hz), 131.5 (C, q, *J* = 30.4 Hz), 131.2 (2 x CH, d, *J* = 8.3 Hz), 127.2 (C, d, *J* = 3.5 Hz), 122.9 (C, q, *J* = 273.2 Hz), 115.7 (CH, d, *J* = 21.7 Hz), 59.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.5 (3F, s), –112.2 (1F, s); HRMS (EI) Exact mass calcd for $C_{10}H_8F_4O$ $[M^+]$: 220.0506, found: 220.0508.



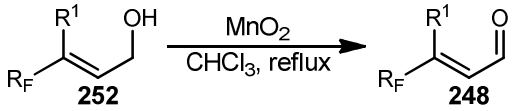
(*Z*)-4,4,4-Trifluoro-3-(thiophen-2-yl)but-2-en-1-ol (252d). The title compound was prepared according to General Procedure D from ester **251d** (4.75 g, 19.0 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil (2.74 g, 69%). R_f = 0.16 (20% EtOAc/hexane); IR (film) 3333 (OH), 1287, 1229, 1175, 1121, 1086, 1028, 849, 837, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 7.09 (1H, dd, *J* = 5.1, 3.4 Hz, Ar**H**), 7.06 (1H, app d, *J* = 3.4 Hz, Ar**H**), 6.61 (1H, tq, *J* = 6.1, 1.5 Hz, =C**H**), 4.38 (2H, dq, *J* = 6.1, 2.1 Hz, C$\mathbf{H}_2$), 1.84 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 136.4 (CH, q, *J* = 5.2 Hz), 130.9 (C), 129.4 (CH), 127.6 (CH), 127.2 (CH), 125.3 (C, q, *J* = 31.3 Hz), 122.5 (C, q, *J* = 273.6 Hz), 59.4 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); HRMS (EI) Exact mass calcd for $C_8H_7F_3OS$ $[M^+]$: 208.0164, found: 208.0160.



(*E*)-5-Phenyl-3-(trifluoromethyl)pent-2-en-1-ol (252e).[101c)] The title compound was prepared according to General Procedure D from ester **251e** (2.54 g, 9.33 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a colourless oil (1.70 g, 79%). R_f = 0.21 (20% EtOAc/hexane); IR (film) 3337 (OH), 1314, 1296, 1209, 1184, 1163, 1109, 1005, 748, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

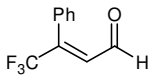
7.34-7.31 (2H, m, Ar**H**), 7.26-7.23 (1H, m, Ar**H**), 7.20-7.19 (2H, m, Ar**H**), 6.25-6.22 (1H, m, =C**H**), 3.83 (2H, d, *J* = 5.0 Hz, C**H**$_2$), 2.80 (2H, t, *J* = 7.5 Hz, C**H**$_2$CH$_2$), 2.53 (2H, t, *J* = 7.5 Hz, CH$_2$C**H**$_2$), 1.09 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.4 (C), 133.9 (CH, q, *J* = 5.9 Hz), 129.3 (C, q, *J* = 28.3 Hz), 128.9 (2 x CH), 128.5 (2 x CH), 126.4 (CH), 124.2 (C, q, *J* = 273.8 Hz), 58.2 (CH_2), 34.6 (CH_2), 27.9 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.0 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{13}F_3O$ [M^+]: 230.0913, found: 230.0914.

General Procedure E: Oxidation of *β*-Perfluoroalkyl Allylic Alcohols

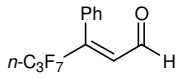


252 **248**

To a solution of the appropriate allylic alcohol (1.0 equiv) in $CHCl_3$ (0.3 M) was added MnO_2 (4.0 equiv) in one portion. The mixture was heated under reflux until complete consumption of the allylic alcohol as observed by TLC analysis. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, washing with the pad with $CHCl_3$. Removal of the solvent under reduced pressure gave the enal of sufficient purity for use in enantioselective arylations.

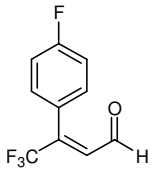


(*E*)-4,4,4-Trifluoro-3-phenylbut-2-enal (248a). The title compound was prepared according to General Procedure E from allylic alcohol **252a** (1.82 g, 9.00 mmol) for 5.5 h to give a yellow oil (1.24 g, 69%). R_f = 0.56 (20% EtOAc/hexane); IR (film) 1692 (C=O), 1356, 1271, 1256, 1180, 1134, 1105, 756, 708, 683 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (1H, d, *J* = 7.5 Hz, C**H**=O), 7.56-7.48 (3H, m, Ar**H**), 7.40 (2H, d, *J* = 7.3 Hz, Ar**H**), 6.65 (1H, dq, *J* = 7.5, 1.1 Hz, =C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.7 (CH), 147.9 (C, q, *J* = 31.6 Hz), 130.8 (CH, q, *J* = 4.9 Hz), 130.5 (CH), 129.9 (2 x CH), 128.8 (2 x CH), 128.7 (C), 122.7 (C, q, *J* = 275.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.4 (3F, s); HRMS (CI) Exact mass calcd for $C_{10}H_8F_3O$ [M+H]$^+$: 201.0522, found: 201.0524.

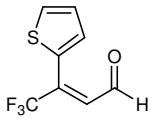


(*E*)-4,4,5,5,6,6,6-Heptafluoro-3-phenylhex-2-enal (248b). The title compound was prepared according to General Procedure E from allylic alcohol **252b** (5.09 g, 16.9 mmol) for 2 h to give a yellow oil (4.18 g, 83%). R_f = 0.69 (20% EtOAc/hexane); IR (film) 1692 (C=O), 1231, 1200, 1182, 1159, 1117, 1101, 976, 731, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (1H, dt, *J* = 7.4, 0.9 Hz, C**H**=O), 7.55-7.46 (3H, m,

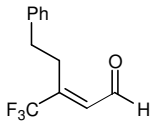
Ar**H**), 7.37 (2H, app d, *J* = 6.9 Hz, Ar**H**), 6.65 (1H, dt, *J* = 7.4, 1.1 Hz, =C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.2 (CH), 147.8 (C, t, *J* = 22.2 Hz), 134.2 (CH, t, *J* = 7.6 Hz), 130.4 (CH), 130.3 (2 x CH), 129.0 (C), 128.6 (2 x CH), 117.6 (C, qt, *J* = 286.1, 33.8 Hz), 114.0 (C, tt, *J* = 256.6, 31.1 Hz), 108.9 (C, tq, *J* = 264.5, 37.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.3 (3F, t, *J* = 10.6 Hz), –113.1 (2F, t, *J* = 10.6 Hz), –124.5 (2F, app s); HRMS (CI) Exact mass calcd for $C_{12}H_8F_7O$ $[M+H]^+$: 301.0458, found: 301.0461.



(*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)but-2-enal (248c). The title compound was prepared according to General Procedure E from allylic alcohol **252c** (3.27 g, 14.9 mmol) for 2.5 h to give a yellow oil (2.74 g, 85%). R_f = 0.64 (20% EtOAc/hexane); IR (film) 1694 (C=O), 1607, 1512, 1275, 1233, 1184, 1169, 1132, 1103, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (1H, d, *J* = 6.9 Hz, C**H**=O), 7.41 (2H, dd, *J* = 8.1, 5.4 Hz, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 6.65 (1H, d, *J* = 6.9 Hz, =C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.2 (CH), 164.0 (C, d, *J* = 252.2 Hz), 146.7 (C, qd, *J* = 32.0, 3.3 Hz), 132.0 (2 x CH, d, *J* = 8.6 Hz), 131.1 (CH, q, *J* = 4.8 Hz), 124.7 (C, d, *J* = 3.5 Hz), 122.6 (C, q, *J* = 275.0 Hz), 116.2 (2 x CH, d, *J* = 22.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.6 (3F, s), –109.1 (1F, s); HRMS (EI) Exact mass calcd for $C_{10}H_5F_4O$ $[M–H]^+$: 217.0271, found: 217.0274.



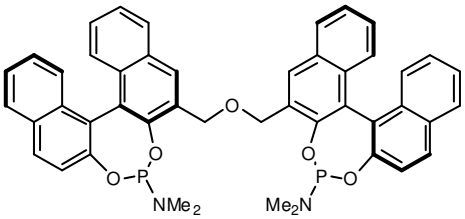
(*Z*)-4,4,4-Trifluoro-3-(thiophen-2-yl)but-2-enal (248d). The title compound was prepared according to General Procedure E from allylic alcohol **252d** (2.64 g, 12.7 mmol) for 1.5 h to give a red oil (2.22 g, 85%). R_f = 0.55 (20% EtOAc/hexane); IR (film) 1682 (C=O), 1271, 1231, 1182, 1128, 1098, 870, 853, 845, 710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (1H, dq, *J* = 7.2, 0.6 Hz, C**H**=O), 7.64 (1H, dd, *J* = 5.1, 1.0 Hz, Ar**H**), 7.32 (1H, dd, *J* = 3.6, 1.0 Hz, Ar**H**), 7.18 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 6.65 (1H, dq, *J* = 7.2, 1.0 Hz, =C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.2 (CH), 140.3 (C, q, *J* = 32.7 Hz), 133.2 (CH), 131.0 (CH), 130.5 (CH, q, *J* = 4.8 Hz), 128.7 (C), 127.9 (CH), 122.3 (C, q, *J* = 275.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.6 (3F, s); HRMS (EI) Exact mass calcd for $C_8H_4F_3OS$ $[M–H]^+$: 204.9929, found: 204.9927.



(*E*)-5-Phenyl-3-(trifluoromethyl)pent-2-enal (248e). The title compound was prepared according to General Procedure E from allylic alcohol **252e** (1.61 g, 7.00 mmol) for 2.5 h to give a yellow oil (1.34 g, 84%). R_f = 0.59 (20%

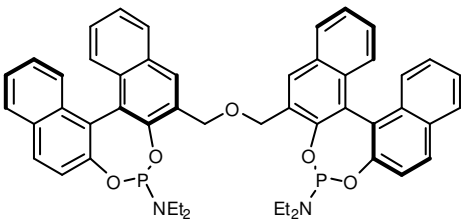
EtOAc/hexane); IR (film) 1690 (C=O), 1310, 1275, 1190, 1167, 1155, 1119, 872, 748, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.49 (1H, d, *J* = 7.1 Hz, C**H**=O), 7.34-7.30 (2H, m, Ar**H**), 7.27-7.23 (1H, m, Ar**H**), 7.18-7.15 (2H, m, Ar**H**), 6.38 (1H, dq, *J* = 7.1, 1.3 Hz, =C**H**), 2.96-2.94 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 189.1 (CH), 145.6 (C, q, *J* = 29.7 Hz), 138.8 (C), 130.4 (CH, q, *J* = 5.4 Hz), 128.8 (4 x CH), 126.9 (CH), 123.6 (C, q, *J* = 273.8 Hz), 35.2 (CH_2), 28.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –68.8 (3F, s); HRMS (EI) Exact mass calcd for $C_{12}H_{11}F_3O$ [M^+]: 228.0757, found: 228.0760.

Preparation of Chiral Ligand 228.



(*R*)-Me-Bipam (228)[171]

The title compound was made according to a literature procedure.[171] To a solution of 3,3''-(Oxydimethylene)-di-1,1'-bi-2-naphthol (123 mg, 0.20 mmol) and NH_4Cl (5 mg) in toluene was added hexamethylphosphoramide (0.10 mL, 0.56 mmol). The mixture was heated at reflux for 16 h. After cooling to rt, the solvent was removed and the residue was recrystallised from hexane/CH_2Cl_2 to give an off-white solid (109 mg, 72 %). $[\alpha]_D^{24}$ – 574.9 (*c* 0.48, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (2H, s, Ar**H**), 7.99-7.91 (6H, m, Ar**H**), 7.52-7.23 (14H, m, Ar**H**), 5.14 (2H, d, *J* = 13.6 Hz, C$\mathbf{H}_2$), 4.95 (2H, d, *J* = 13.6 Hz, C$\mathbf{H}_2$), 2.48 (12H, d, *J* = 8.9 Hz, NC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.8 (2 x C), 150.1 (2 x C), 149.3 (2 x C), 132.8 (2 x C), 132.0 (2 x C), 131.4 (2 x C), 130.3 (2 x CH), 128.34 (2 x CH), 128.33 (2 x CH), 128.2 (2 x C), 126.93 (2 x CH), 126.89 (2 x C), 126.8 (2 x CH), 126.1 (2 x CH), 125.9 (2 x CH), 124.81 (2 x CH), 124.79 (2 x CH), 124.6 (2 x C), 122.0 (2 x CH), 121.8 (2 x CH), 68.9 (2 x CH_2), 34.7 (4 x CH_3); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 149.0 (2P, s).

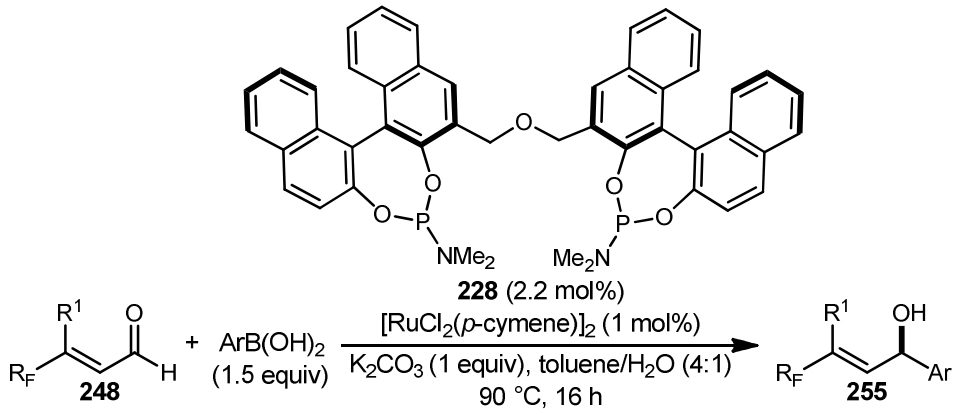


(*R*)-Et-Bipam (264)[172]

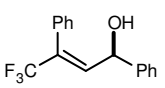
The title compound was made according to a literature procedure.[172] To a solution of 3,3''-(Oxydimethylene)-di-1,1'-bi-2-naphthol (123 mg, 0.20 mmol) and NH_4Cl (10 mg) in toluene was added hexaethylphosphoramide (0.15 mL, 0.56 mmol). The mixture was heated at reflux for 16 h. After cooling to rt, the solvent was removed and the residue was purified by column chromatography (10%

EtOAc/hexane) to give a white solid (112 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (2H, d, *J* = 4.1 Hz, Ar**H**), 7.97 (4H, dd, *J* = 8.8, 4.1 Hz, Ar**H**), 7.92 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.51 (2H, dd, *J* = 8.8, 0.7 Hz, Ar**H**), 7.45-7.36 (6H, m, Ar**H**), 7.33-7.21 (6H, m, Ar**H**), 5.16 (2H, d, *J* = 13.9 Hz, OC**H**$_2$), 5.02 (2H, d, *J* = 13.9 Hz, OC**H**$_2$), 2.92 (8H, dm, *J* = 69.6 Hz, PNC**H**$_2$), 1.04-0.86 (12H, m, CH_2C**H**$_3$).

General Procedure F: Enantioselective Arylation of *β*-Perfluoroalkyl-*α*,*β*-Unsaturated Aldehydes

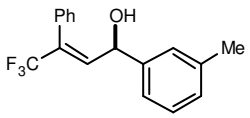


A solution of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mg, 0.004 mmol) and **228** (8.4 mg, 0.011 mmol) in toluene (1.2 mL) was stirred at room temperature for 30 min. To this solution was added a solution of the appropriate enal (0.50 mmol), K_2CO_3 (69.1 mg, 0.50 mmol) and the appropriate boronic acid (0.75 mmol) in toluene (1.2 mL) and H_2O (0.6 mL) *via* cannula and the mixture was heated at 90 °C for 16 h. After cooling to room temperature, the mixture was partitioned between saturated aqueous NH_4Cl solution (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the allylic alcohol.

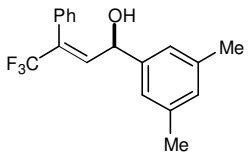


(*R*)-(*E*)-4,4,4-Trifluoro-1,3-diphenylbut-2-en-1-ol (255a).[57] The title compound was prepared according to General Procedure F from enal **248a** (100 mg, 0.50 mmol) and phenylboronic acid (91 mg, 0.75 mmol) to give a colourless oil (93 mg, 66%). Spectral data were consistent with those reported previously.[57] $[\alpha]_D^{24}$ –134.0 (*c* 0.99, $CHCl_3$), Lit[57] $[\alpha]_D^{20}$ +136.0 (*c* 1.6, $CHCl_3$) for (*S*)-isomer of 76% ee; R_f = 0.45 (20% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (3H, m, Ar**H**), 7.39-7.26 (7H, m, Ar**H**), 6.62 (1H, dq, *J* = 9.3, 1.4 Hz, =C**H**), 5.14 (1H, br d, *J* = 9.3 Hz, C**H**OH), 1.95 (1H, d, *J*

= 3.4 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.5 (C), 136.5 (CH, q, *J* = 5.2 Hz), 132.1 (C, q, *J* = 30.3 Hz), 131.3 (C), 129.6 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 128.6 (2 x CH), 128.4 (CH), 126.2 (2 x CH), 123.1 (C, q, *J* = 273.5 Hz), 70.4 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 8.5 min; t_r (minor) = 10.2 min, 84% ee.

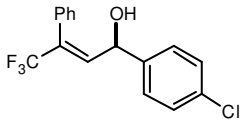


(*R*)-(*E*)-4,4,4-Trifluoro-1-(3-methylphenyl)-3-phenylbut-2-en-1-ol (255b). The title compound was prepared according to General Procedure F from enal **248a** (100 mg, 0.50 mmol) and 3-tolylboronic acid (102 mg, 0.75 mmol) to give a colourless oil (94 mg, 64%). $[\alpha]_D^{24}$ –120.2 (*c* 0.87, $CHCl_3$); R_f = 0.39 (20% EtOAc/hexane); IR (film) 3360 (OH), 1283, 1233, 1171, 1121, 1074, 1024, 791, 752, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.42 (3H, m, Ar**H**), 7.29 (2H, dd, *J* = 6.4, 2.9 Hz, Ar**H**), 7.25 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.13 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.09 (1H, s, Ar**H**), 7.04 (1H, d, *J* = 7.6 Hz, Ar**H**), 6.62 (1H, dq, *J* = 9.3, 1.4 Hz, =C**H**), 5.10 (1H, dd, *J* = 9.3, 3.4 Hz, C**H**OH), 2.36 (3H, s, C**H**$_3$), 1.94-1.93 (1H, m, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.5 (C), 138.7 (C), 136.6 (CH, q, *J* = 5.3 Hz), 132.0 (C, q, *J* = 30.3 Hz), 131.4 (C), 129.7 (2 x CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.5 (2 x CH), 126.8 (CH), 123.2 (CH), 123.1 (C, q, *J* = 273.5 Hz), 70.4 (CH), 21.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{15}F_3O$ [M^+]: 292.1070, found: 292.1063. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 9.1 min; t_r (minor) = 11.2 min, 85% ee.

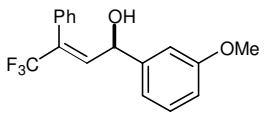


(*R*)-(2E)-3-(3,5-Dimethylphenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (255c). The title compound was prepared according to General Procedure F from enal **248a** (100 mg, 0.50 mmol) and 3,5-dimethylphenylboronic acid (112 mg, 0.75 mmol) to give a pale yellow solid (95 mg, 62%). m.p. 48-50 °C; $[\alpha]_D^{24}$ –183.3 (*c* 0.72, $CHCl_3$); R_f = 0.42 (20% EtOAc/hexane); IR (film) 3337 (OH), 1512, 1315, 1269, 1236, 1173, 1123, 1011, 845, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.43 (3H, m, Ar**H**), 7.30-7.29 (2H, m, Ar**H**), 6.97 (1H, s, Ar**H**), 6.87 (2H, s, Ar**H**), 6.63 (1H, dq, *J* = 9.2, 1.4 Hz, =C**H**), 5.06 (1H, dd, *J* = 9.2, 3.4 Hz, C**H**OH), 2.32 (6H, s, ArC**H**$_3$), 1.90 (1H, d, *J* = 3.4 Hz, O**H**); ^{13}C NMR (125.8 MHz,

$CDCl_3$) δ 141.5 (C), 138.5 (2 x C), 136.7 (CH, q, *J* = 5.3 Hz), 131.9 (C, q, *J* = 30.3 Hz), 131.4 (C), 130.0 (CH), 129.7 (2 x CH), 129.0 (CH), 128.5 (2 x CH), 123.9 (2 x CH), 123.1 (C, q, *J* = 273.6 Hz), 70.4 (CH), 21.3 (2 x CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.5 (3F, s); HRMS (EI) Exact mass calcd for $C_{18}H_{17}F_3O$ [M^+]: 306.1226, found: 306.1227. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (minor) = 9.8 min; t_r (major) = 13.3 min, 84% ee.

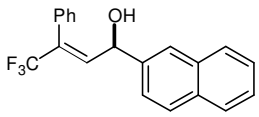


(*R*)-(*E*)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (255d). The title compound was prepared according to General Procedure F from enal **248a** (100 mg, 0.50 mmol) and 4-chlorophenylboronic acid (117 mg, 0.75 mmol) to give a colourless oil which solidified upon standing to give a white amorphous solid (105 mg, 66%). $[\alpha]_D^{24}$ –216.6 (*c* 0.91, $CHCl_3$); R_f = 0.48 (20% EtOAc/hexane); IR (film) 3279 (OH), 1491, 1312, 1279, 1240, 1171, 1126, 1028, 1013, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (3H, m, Ar**H**), 7.34-7.32 (2H, m, Ar**H**), 7.27-7.25 (2H, m, Ar**H**), 7.20-7.18 (2H, m, Ar**H**), 6.55 (1H, dq, *J* = 9.1, 1.4 Hz, =C**H**), 5.12 (1H, dd, *J* = 9.1, 2.8 Hz, C**H**OH), 1.99 (1H, d, *J* = 2.8 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.0 (C), 136.1 (CH, q, *J* = 5.3 Hz), 134.1 (C), 132.5 (C, q, *J* = 30.5 Hz), 131.1 (C), 129.5 (2 x CH), 129.2 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 127.5 (2 x CH), 122.9 (C, q, *J* = 273.6 Hz), 69.8 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.4 (3F, s); HRMS (CI) Exact mass calcd for $C_{16}H_{11}F_3OCl$ [M–H]$^+$: 311.0445, found: 311.0444. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 8.5 min; t_r (minor) = 10.0 min, 87% ee.

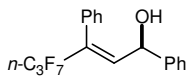


(*R*)-(*E*)-4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-phenylbut-2-en-1-ol (255e). The title compound was prepared according to General Procedure F from enal **248a** (100 mg, 0.50 mmol) and 3-methoxyphenylboronic acid (114 mg, 0.75 mmol) to give a yellow oil (77 mg, 50%). $[\alpha]_D^{24}$ –152.0 (*c* 1.00, $CHCl_3$); R_f = 0.23 (20% EtOAc/hexane); IR (film) 3374 (OH), 1317, 1258, 1171, 1119, 1036, 1026, 905, 779, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (3H, m, Ar**H**), 7.30-7.26 (3H, m, Ar**H**), 6.86-6.82 (3H, m, Ar**H**), 6.59 (1H, dq, *J* = 9.2, 1.4 Hz, =C**H**), 5.11 (1H, d, *J* = 9.2 Hz, C**H**OH), 3.81 (3H, s, OC**H**$_3$), 2.00 (1H, d, *J* = 1.8 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.9 (C), 143.1 (C), 136.4 (CH, q, *J* = 5.3 Hz), 132.1 (C, q, *J* = 30.3 Hz), 131.3 (C), 129.9 (CH), 129.7 (2 x CH), 129.0 (CH), 128.6 (2 x CH), 123.1

(C, q, J = 273.6 Hz), 118.3 (CH), 113.8 (CH), 111.7 (CH), 70.3 (CH), 55.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{15}F_3O_2$ [M^+]: 308.1019, found: 308.1018. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (minor) = 21.3 min; t_r (major) = 29.6 min, 79% ee.

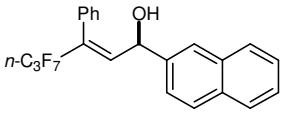


(*R*)-(*E*)-4,4,4-Trifluoro-1-(naphthalene-2-yl)-3-phenylbut-2-en-1-ol (255f). The title compound was prepared according to General Procedure F from enal **248a** (100 mg, 0.50 mmol) and 2-naphthyleneboronic acid (129 mg, 0.75 mmol) to give a pale yellow oil (107 mg, 64%). $[\alpha]_D^{24}$ –163.6 (*c* 1.21, $CHCl_3$); R_f = 0.37 (20% EtOAc/hexane); IR (film) 3319 (OH), 1310, 1271, 1256, 1171, 1119, 858, 820, 752, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89-7.82 (3H, m, Ar**H**), 7.69 (1H, s, Ar**H**), 7.53-7.50 (2H, m, Ar**H**), 7.47-7.45 (3H, m, Ar**H**), 7.40 (1H, dd, J = 8.5, 1.7 Hz, Ar**H**), 7.32 (2H, dd, J = 6.5, 2.9 Hz, Ar**H**), 6.72 (1H, dq, J = 9.2, 1.4 Hz, =C**H**), 5.32 (1H, dd, J = 9.2, 2.0 Hz, C**H**OH), 2.08 (1H, d, J = 3.4 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.9 (C), 136.4 (CH, q, J = 5.3 Hz), 133.3 (C), 133.2 (C), 132.3 (C, q, J = 30.3 Hz), 131.4 (C), 129.7 (2 x CH), 129.1 (CH), 128.8 (CH), 128.6 (2 x CH), 128.0 (CH), 127.7 (CH), 126.44 (CH), 126.37 (CH), 125.1 (CH), 124.0 (CH), 123.1 (C, q, J = 274.0 Hz), 70.6 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{20}H_{15}F_3O$ [M^+]: 328.1070, found: 328.1063. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (major) = 21.0 min; t_r (minor) = 33.4 min, 85% ee.

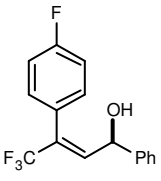


(*R*)-(*E*)-4,4,5,5,6,6,6-Heptafluoro-1,3-diphenylhex-2-en-1-ol (255g). The title compound was prepared according to General Procedure F from enal **248b** (150 mg, 0.50 mmol) and phenylboronic acid (91 mg, 0.75 mmol) to give a yellow oil (114 mg, 66%). $[\alpha]_D^{24}$ –106.3 (*c* 1.43, $CHCl_3$); R_f = 0.49 (20% EtOAc/hexane); IR (film) 3332 (OH), 1344, 1227, 1180, 1138, 1113, 1016, 976, 718, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.30 (6H, m, Ar**H**), 7.26-7.23 (4H, m, Ar**H**), 6.65 (1H, dt, J = 9.1, 1.0 Hz, =C**H**), 5.12 (1H, dd, J = 9.1, 3.7 Hz, C**H**OH), 1.95 (1H, d, J = 3.7 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.5 (C), 140.3 (CH, t, J = 8.1 Hz), 131.5 (C), 131.3 (C, t, J = 21.7 Hz), 130.1 (2 x CH), 128.94 (CH), 128.86 (2 x CH), 128.39 (2 x CH), 128.35 (CH), 126.2 (2 x CH), 117.9 (C, qt, J = 288.3, 34.5 Hz), 114.2 (C, tt, J = 256.4, 31.1 Hz), 109.2 (C, tq, J =

265.7, 37.9), 70.5 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, *J* = 10.6 Hz), –(110.2-111.8) (2F, m), –124.4 (2F, app s); HRMS (EI) Exact mass calcd for $C_{18}H_{13}F_7O$ [M^+]: 378.0849, found: 378.0852. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (99:1 hexane:*i*-PrOH, 1.0 mL/min, 230 nm); t_r (major) = 13.9 min; t_r (minor) = 14.5 min, 86% ee.

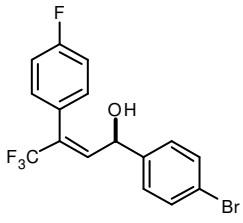


(*R*)-(*E*)-4,4,5,5,6,6,6-Heptafluoro-1-(naphthalen-2-yl)-3-phenylhex-2-en-1-ol (255h). The title compound was prepared according to General Procedure F from enal **248b** (150 mg, 0.50 mmol) and 2-naphthylboronic acid (129 mg, 0.75 mmol) to give a pale yellow oil (112 mg, 52%). $[\alpha]_D^{24}$ –176.2 (*c* 0.97, $CHCl_3$); R_f = 0.49 (20% EtOAc/hexane); IR (film) 3337 (OH), 1342, 1227, 1211, 1180, 1113, 980, 745, 710, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.81 (3H, m, Ar**H**), 7.65 (1H, br s, Ar**H**), 7.52-7.50 (2H, m, Ar**H**), 7.45-7.37 (4H, m, Ar**H**), 7.28-7.26 (2H, m, Ar**H**), 6.74 (1H, dt, *J* = 9.0, 1.4 Hz, =C**H**), 5.29 (1H, d, *J* = 9.0 Hz, C**H**OH), 2.07 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.2 (CH, t, *J* = 8.1 Hz), 138.8 (C), 133.21 (C), 133.15 (C), 131.6 (C), 131.4 (C, t, *J* = 21.5 Hz), 130.1 (2 x CH), 129.0 (CH), 128.8 (CH), 128.4 (2 x CH), 128.0 (CH), 127.7 (CH), 126.41 (CH), 126.36 (CH), 125.2 (CH), 124.0 (CH), 117.9 (C, qt, *J* = 288.4, 34.7 Hz), 114.2 (C, tt, *J* = 257.0, 30.7 Hz), 109.2 (C, tq, *J* = 265.9, 38.1 Hz), 70.7 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.4 (3F, t, *J* = 10.2 Hz), –(110.2-111.9) (2F, m), –124.4 (2F, app s); HRMS (EI) Exact mass calcd for $C_{22}H_{15}F_7O$ [M^+]: 428.1006, found: 428.1008. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 20.2 min; t_r (minor) = 30.5 min, 76% ee.

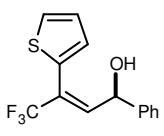


(*R*)-(*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)-1-phenyl-but-2-en-1-ol (255i). The title compound was prepared according to General Procedure F from enal **248c** (109 mg, 0.50 mmol) and phenylboronic acid (91 mg, 0.75 mmol) to give a colourless oil which solidified upon standing to give a beige amorphous solid (90 mg, 60%). $[\alpha]_D^{24}$ –168.9 (*c* 1.13, $CHCl_3$); R_f = 0.31 (20% EtOAc/hexane); IR (film) 3341 (OH), 1512, 1310, 1229, 1171, 1121, 1015, 841, 737, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (3H, m, Ar**H**), 7.28-7.25 (4H, m, Ar**H**), 7.16-7.11 (2H, m, Ar**H**), 6.65 (1H, dq, *J* = 9.1, 1.4 Hz, =C**H**), 5.11 (1H, br d, *J* = 9.1 Hz, C**H**OH), 2.03 (1H, br m, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.1 (C, d, *J* = 249.0), 141.4 (C), 137.1 (CH, q, *J* = 5.2 Hz), 131.6 (2

x CH, d, *J* = 8.3 Hz), 131.1 (C, q, *J* = 30.5 Hz), 129.0 (2 x CH), 128.5 (CH), 127.2 (C, d, *J* = 3.5 Hz), 126.2 (2 x CH), 122.9 (C, q, *J* = 274.3 Hz), 115.7 (2 x CH, d, *J* = 21.7 Hz), 70.5 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.7 (3F, s), –112.1 (1F, s); HRMS (EI) Exact mass calcd for $C_{16}H_{12}F_4O$ [M^+]: 296.0819, found: 296.0815. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 10.7 min; t_r (minor) = 13.1 min, 81% ee.

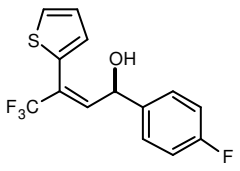


(*R*)-(*E*)-1-(4-Bromophenyl)-4,4,4-trifluoro-3-(4-fluorophenyl)but-2-en-1-ol (255j). The title compound was prepared according to General Procedure F from enal **248c** (109 mg, 0.50 mmol) and 4-bromophenylboronic acid (151 mg, 0.75 mmol) to give a pale yellow oil (115 mg, 61%). [α] $^{24}_{D}$ –208.6 (*c* 0.58, $CHCl_3$); R_f = 0.29(20% EtOAc/hexane); IR (film) 3335 (OH), 1512, 1229, 1171, 1123, 1009, 928, 841, 814, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.49 (2H, m, Ar**H**), 7.26-7.23 (2H, m, Ar**H**), 7.16-7.11 (4H, m, Ar**H**), 6.58 (1H, dq, *J* = 9.1, 1.5 Hz, =C**H**), 5.08 (1H, dd, *J* = 9.1, 3.5 Hz, C**H**OH), 1.98 (1H, d, *J* = 3.5 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.2 (C, d, *J* = 249.4 Hz), 140.3 (C), 136.6 (CH, q, *J* = 5.1 Hz), 132.1 (2 x CH), 131.6 (C, q, *J* = 30.6 Hz), 131.5 (2 x CH, d, *J* = 8.3 Hz), 127.8 (2 x CH), 127.0 (C, d, *J* = 3.5 Hz), 122.8 (C, q, *J* = 273.8 Hz), 122.5 (C), 115.9 (2 x CH, d, *J* = 21.7 Hz), 69.9 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.9 (3F, s), –111.8 (1F, s); HRMS (EI) Exact mass calcd for $C_{16}H_{11}F_4OBr$ [M^+]: 373.9924, found: 373.9918. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 230 nm); t_r (major) = 10.3 min; t_r (minor) = 12.7 min, 84% ee.

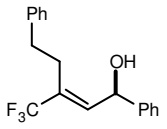


(*R*)-(*Z*)-4,4,4-Trifluoro-1-phenyl-3-(thiophen-2-yl)but-2-en-1-ol (255k). The title compound was prepared according to General Procedure F from enal **248d** (103 mg, 0.50 mmol) and phenylboronic acid (91 mg, 0.75 mmol) to give a pale yellow oil (101 mg, 71%). [α] $^{24}_{D}$ –180.0 (*c* 1.00, $CHCl_3$); R_f = 0.41 (20% EtOAc/hexane); IR (film) 3345 (OH), 1306, 1287, 1277, 1229, 1175, 1123, 1015, 764, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.47 (1H, m, Ar**H**), 7.42-7.33 (5H, m, Ar**H**), 7.11 (2H, d, *J* = 3.6 Hz, Ar**H**), 6.69 (1H, dq, *J* = 9.2, 1.4 Hz, =C**H**), 5.46 (1H, d, *J* = 9.2 Hz, C**H**OH), 2.10 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.2 (C), 138.5 (CH, q, *J* = 5.0 Hz), 130.5 (C), 129.9 (CH), 128.9 (2 x CH), 128.5 (CH), 127.9 (CH), 127.3 (CH), 126.3

(2 x CH), 125.5 (C, q, *J* = 31.5 Hz), 122.6 (C, q, *J* = 273.8 Hz), 70.3 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.9 (3F, s); HRMS (EI) Exact mass calcd for $C_{14}H_{11}F_3OS$ [M^+]: 284.0477, found: 284.0480. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 10.9 min; t_r (minor) = 13.3 min, 85% ee.

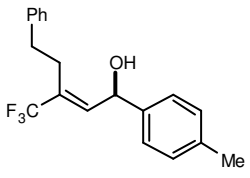


(*R*)-(*Z*)-4,4,4-Trifluoro-1-(4-fluorophenyl)-3-(thiophen-2-yl)but-2-en-1-ol (255l). The title compound was prepared according to General Procedure F from enal **248d** (103 mg, 0.50 mmol) and 4-fluorophenylboronic acid (105 mg, 0.75 mmol) to give a pale brown oil (89 mg, 59%). $[\alpha]_D^{24}$ –149.8 (*c* 1.14, $CHCl_3$); R_f = 0.34 (20% EtOAc/hexane); IR (film) 3345 (OH), 1310, 1227, 1175, 1157, 1125, 1013, 835, 704, 563 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1H, dd, *J* = 5.0, 1.4 Hz, Ar**H**), 7.36-7.31 (2H, m, Ar**H**), 7.12-7.06 (4H, m, Ar**H**), 6.65 (1H, dq, *J* = 9.1, 1.4 Hz, =C**H**), 5.45 (1H, d, *J* = 9.1 Hz, C**H**OH), 2.07 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.6 (C, d, *J* = 247.3 Hz), 138.3 (CH, q, *J* = 4.9 Hz), 137.0 (C, d, *J* = 3.1 Hz), 130.3 (C), 129.8 (CH), 128.1 (2 x CH, d, *J* = 8.2 Hz), 127.9 (CH), 127.3 (CH), 125.7 (C, q, *J* = 31.7 Hz), 122.5 (C, q, *J* = 273.8 Hz), 115.8 (2 x CH, d, *J* = 21.6 Hz), 69.7 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.0 (3F, s), –113.5 (1F, s); HRMS (EI) Exact mass calcd for $C_{14}H_{10}F_4OS$ [M^+]: 302.0383, found: 302.0381. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 10.6 min; t_r (minor) = 12.8 min, 87% ee.



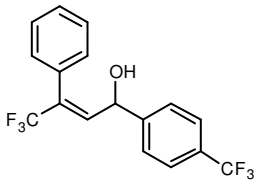
(*R*)-(*E*)-1,5-Diphenyl-3-(trifluoromethyl)pent-2-en-1-ol (255m). The title compound was prepared according to General Procedure F from enal **248e** (114 mg, 0.50 mmol) and phenylboronic acid (91 mg, 0.75 mmol) to give a pale yellow oil (61 mg, 40%). $[\alpha]_D^{24}$ –60.7 (*c* 0.89, $CHCl_3$); R_f = 0.47 (20% EtOAc/hexane); IR (film) 3370 (OH), 1325, 1186, 1163, 1113, 1003, 762, 746, 698, 552 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.23 (10H, m, Ar**H**), 6.26 (1H, dq, *J* = 9.1, 1.3 Hz, =C**H**), 5.09 (1H, d, *J* = 9.1 Hz, C**H**OH), 2.86-2.83 (2H, m, C**H**$_2$CH$_2$), 2.74-2.63 (2H, m, CH$_2$C**H**$_2$), 1.28 (1H, br s, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.1 (C), 140.6 (C), 136.5 (CH, q, *J* = 5.7 Hz), 129.0 (C, q, *J* = 28.1 Hz), 128.9 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.1 (CH), 126.6 (CH), 125.9 (2 x CH), 124.3 (C, q, *J* = 274.3 Hz), 69.5 (CH), 34.6 (CH_2), 28.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{18}H_{17}F_3O$ [M^+]:

306.1226, found: 306.1229. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 210 nm); t_r (major) = 17.1 min; t_r (minor) = 21.0 min, 79% ee.



(*R*)-(*E*)-1-(4-Methylphenyl)-5-phenyl-3-(trifluoromethyl)pent-2-en-1-ol (255n)

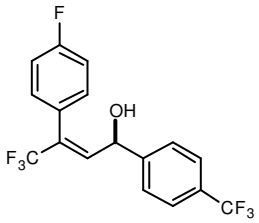
The title compound was prepared according to General Procedure F from enal **248e** (114 mg, 0.50 mmol) and 4-tolylboronic acid (102 mg, 0.75 mmol) to give a pale yellow oil (67 mg, 42%). $[\alpha]_D^{24}$ –119.2 (*c* 0.99, $CHCl_3$); R_f = 0.46 (20% EtOAc/hexane); IR (film) 3356 (OH), 1314, 1229, 1184, 1161, 1113, 1003, 818, 748, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.35 (2H, m, Ar**H**), 7.29-7.23 (3H, m, Ar**H**), 7.17-7.13 (4H, m, Ar**H**), 6.28 (1H, dq, *J* = 9.0, 1.1 Hz, =C**H**), 5.09 (1H, dd, *J* = 9.0, 2.8 Hz, C**H**OH), 2.83 (2H, t, *J* = 7.6 Hz, C**H**$_2$CH$_2$), 2.72-2.62 (2H, m, CH$_2$C**H**$_2$), 2.35 (3H, s, C**H**$_3$), 1.27 (1H, dd, *J* = 2.8, 1.5 Hz, O**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.7 (C), 138.3 (C), 138.0 (C), 136.7 (CH, q, *J* = 5.8 Hz), 129.4 (2 x CH), 128.9 (2 x CH), 128.8 (C, q, *J* = 27.9 Hz), 128.6 (2 x CH), 126.6 (CH), 125.9 (2 x CH), 124.3 (C, q, *J* = 274.3 Hz), 69.4 (CH), 34.6 (CH$_2$), 28.0 (CH$_2$), 21.1 (CH$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.6 (3F, s); HRMS (EI) Exact mass calcd for $C_{19}H_{19}F_3O$ [M^+]: 320.1383, found: 320.1382. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (major) = 13.7 min; t_r (minor) = 16.1 min, 85% ee.



(2*E*)-4,4,4-Trifluoro-3-phenyl-1-[4-(trifluoromethyl)phenyl]but-2-en-1-ol (255q)

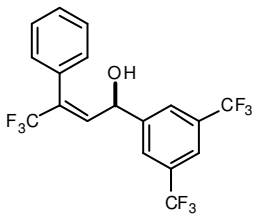
The title compound was prepared according to General Procedure F from enal **248a** (100 mg, 0.50 mmol) and 4-trifluoromethylphenylboronic acid (142 mg, 0.75 mmol) to give a pale yellow oil which solidified upon standing to give a pale yellow amorphous solid (65 mg, 38%). R_f = 0.28 (20% EtOAc/hexane); IR (film) 3289 (OH), 1323, 1248, 1171, 1117, 1067, 1042, 1015, 849, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.2 Hz, Ar**H**); 7.48-7.45 (3H, m, Ar**H**), 7.39 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.29 (2H, dd, *J* = 6.5, 2.9 Hz, Ar**H**), 6.56 (1H, dq, *J* = 9.1, 1.4 Hz, C=C**H**), 5.22 (1H, dd, *J* = 9.1, 2.5 Hz, C**H**OH), 2.11 (1H, d, *J* = 3.6 Hz, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2 (C), 135.8 (CH, q, *J* = 5.2 Hz), 133.1 (C, q, *J* = 30.5 Hz), 131.0 (C), 130.5 (C, q, *J* = 32.5 Hz), 129.5 (2 x CH), 129.3 (CH), 128.8 (2 x CH), 126.4 (2 x CH),

125.8 (2 x CH, q, *J* = 3.8 Hz), 123.9 (C, q, *J* = 272.7 Hz), 122.9 (C, q, *J* = 274.3 Hz), 69.8 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.7 (3F, s), –66.7 (3F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{12}F_6O$ [M^+]: 346.07869, found: 346.07892. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 210 nm); t_r = 7.9 min and 9.3 min, 0% ee.



(*R*)-(2*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)-1-[4-(trifluoromethyl)phenyl]but-2-en-1-ol (255r).

The title compound was prepared according to General Procedure F from enal **248c** (109 mg, 0.50 mmol) and 4-trifluoromethylphenylboronic acid (142 mg, 0.75 mmol) to give a pale yellow oil (70 mg, 38%). R_f = 0.42 (20% EtOAc/hexane); IR (film) 3352 (OH), 1512, 1325, 1236, 1171, 1121, 1067, 1016, 843, 814 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.37 (2H, d, J = 8.2 Hz, Ar**H**), 7.25-7.28 (2H, m, Ar**H**), 7.12-7.17 (2H, m, Ar**H**), 6.58 (1H, dq, *J* = 9.1, 1.4 Hz, C=C**H**), 5.18 (1H, dd, *J* = 9.1, 1.5 Hz, C**H**OH), 2.15 (1H, d, *J* = 3.5 Hz, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (C, d, *J* = 249.6 Hz), 145.1 (C), 136.3 (CH, q, *J* = 5.1 Hz), 132.1 (C, q, *J* = 30.7 Hz), 131.5 (2 x CH, d, *J* = 8.4 Hz), 130.6 (C, q, *J* = 32.6 Hz), 126.9 (C, d, *J* = 3.5 Hz), 126.5 (2 x CH), 125.9 (2 x CH, q, *J* = 3.8 Hz), 123.9 (C, q, *J* = 270.5 Hz), 122.8 (C, q, *J* = 271.8 Hz), 116.0 (2 x CH, d, *J* = 21.7 Hz), 69.9 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.8 (3F, s), –67.0 (3F, s), –111.6 (1F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{11}F_7O$ [M^+]: 346.06926, found: 364.07025. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 210 nm); t_r (major) = 10.0 min; t_r (minor) = 11.9 min, 6% ee.



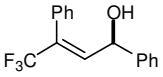
(*R*)-(2*E*)-1-[3,5-bis(trifluoromethyl)phenyl]-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (255s)

The title compound was prepared according to General Procedure B from enal **248a** (100 mg, 0.50 mmol) and 3,5-difluoromethylphenylboronic acid (310 mg, 0.75 mmol) to give a yellow solid (56 mg, 26%). $[\alpha]_D^{24}$ +93.7 (*c* 1.05, $CHCl_3$); m.p. 59-61 °C; R_f = 0.50 (20% EtOAc/hexane); IR (film) 3350 (OH), 1277, 1167, 1126, 1109, 1086, 901, 889, 841, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (1H, app s, Ar**H**), 7.68 (2H, app s, Ar**H**), 7.49-7.47 (3H, m, Ar**H**), 7.28 (2H, dd, *J* = 6.6, 3.0 Hz, Ar**H**), 6.54 (1H, dq, *J* = 8.5, 1.5 Hz, C=C**H**),

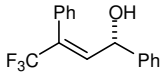
5.31 (1H, dd, *J* = 8.5, 3.6 Hz, C**H**OH), 2.28 (1H, d, *J* = 3.6 Hz, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9 (C), 135.4 (CH, q, *J* = 5.2 Hz), 134.0 (C, q, *J* = 30.8 Hz), 132.1 (2 x C, q, *J* = 33.5 Hz), 130.8 (C), 129.5 (CH), 129.4 (2 x CH), 129.0 (2 x CH), 126.3 (2 x CH, q, *J* = 2.9 Hz), 123.1 (2 x C, q, *J* = 273.3 Hz), 122.7 (C, q, *J* = 274.3 Hz), 122.1 (CH, sept, *J* = 3.8 Hz), 69.4 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.0 (6F, s), –67.1 (3F, s); HRMS (EI) Exact mass calcd for $C_{18}H_{11}F_9O$ [M^+]: 414.06607, found: 414.06683. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 210 nm); t_r (major) = 4.9 min; t_r (minor) = 6.7 min, 54% ee.

Stereochemical Determinations

The absolute stereochemistry of **255a** was assigned as (*R*) by comparison of the optical rotation with that reported for the (*S*)-isomer in the literature.[57]



(*R*)-**2a** (84% ee)
prepared herein



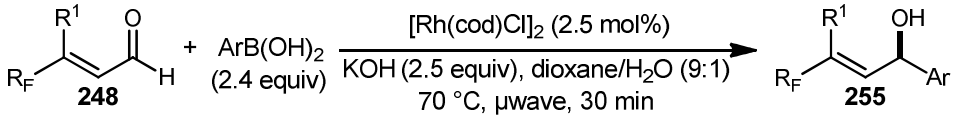
(*S*)-**2a** (76% ee)
literature compound

(*R*)-**255a**: $[\alpha]_D^{24}$ –134.0 (*c* 0.99, $CHCl_3$)

(*S*)-**255a**: $[\alpha]_D^{20}$ +136.0 (*c* 1.6, $CHCl_3$)

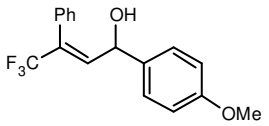
In addition, the sense of enantioinduction in the arylation reaction producing (*R*)-**255a** described herein is consistent with that reported in the literature for similar reactions using ligand **228**. The absolute stereochemistries of the remaining products were assigned by analogy.

General Procedure G: Racemic Arylation of *β*-Perfluoroalkyl-*α*,*β*-Unsaturated Aldehydes



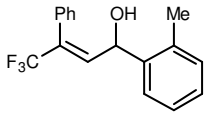
Authentic racemic samples for chiral HPLC assay determinations were prepared using the following procedure: A solution of the appropriate enal (0.5 mmol, 1 equiv), $[Rh(cod)Cl]_2$ (6.2 mg, 0.0125 mmol), KOH (70.1 mg, 1.25 mmol) and the appropriate boronic acid (1.2 mmol, 2.4 equiv) in 9:1 dioxane/H_2O (3 mL) was heated under microwave irradiation at 70 °C for 30 min. After cooling to room temperature, the reaction mixture was filtered through a

plug of SiO_2 using CH_2Cl_2 as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) afforded the desired allylic alcohol.



(2*E*)-4,4,4-trifluoro-1-(methoxyphenyl)-3-phenylbut-2-en-1-ol (255o).

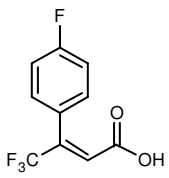
The title compound was prepared according to General Procedure G from enal **248a** (100 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (182 mg, 1.2 mmol) and purified by column chromatography (5→20% EtOAc/hexane) to give a yellow oil (117 mg, 76%). R_f = 0.16 (20% EtOAc/hexane); IR (Neat) 3340 (OH), 1610, 1512, 1304, 1250, 1171, 1121, 1032, 831, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.45 (3H, m, Ar**H**), 7.26-7.28 (2H, m, Ar**H**), 7.18-7.21 (2H, m, Ar**H**), 6.88-6.91 (2H, m, Ar**H**), 6.63 (1H, dq, *J* = 9.2, 1.5 Hz, C=C**H**), 5.09 (1H, dd, *J* = 9.2, 3.1 Hz, C**H**OH), 3.82 (3H, s, OC$\mathbf{H}_3$), 1.88-1.91 (1H, m, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (C), 136.7 (CH, q, *J* = 5.3 Hz), 133.8 (C), 131.6 (C, q, *J* = 30.2 Hz), 131.4 (C), 129.7 (2 x CH), 129.0 (CH), 128.5 (2 x CH), 127.5 (2 x CH), 123.1 (C, q, *J* = 273.5 Hz), 114.3 (2 x CH), 70.0 (CH), 55.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.5 (3F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{15}F_3O_2$ [M^+]: 308.1019, found: 308.1016.



(2*E*)-4,4,4-trifluoro-1-(2-methylphenyl)-3-phenylbut-2-en-1-ol (255p).

The title compound was prepared according to General Procedure G from enal **248a** (100 mg, 0.50 mmol) and 2-tolylboronic acid (163 mg, 1.2 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a yellow oil (99 mg, 68%). R_f = 0.32 (20% EtOAc/hexane); IR (Neat) 3306 (OH), 1308, 1271, 1242, 1171, 1119, 1015, 745, 702, 610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.45 (4H, m, Ar**H**), 7.24-7.28 (3H, m, Ar**H**), 7.22 (1H, td, *J* = 7.2, 1.6 Hz, Ar**H**), 7.12 (1H, d, *J* = 7.2 Hz, Ar**H**), 6.68 (1H, dq, *J* = 9.0, 1.5 Hz, C=C**H**), 5.32 (1H, dd, *J* = 9.0, 3.0 Hz, C**H**OH), 2.00 (3H, s, ArC$\mathbf{H}_3$), 1.87 (1H, d, J = 3.0 Hz, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9 (C), 136.4 (CH, q, *J* = 5.3 Hz), 135.4 (C), 132.3 (C, q, *J* = 30.3 Hz), 131.4 (C), 130.8 (CH), 129.5 (2 x CH), 129.0 (CH), 128.5 (2 x CH), 128.2 (CH), 126.6 (CH), 126.1 (CH), 123.1 (C, q, *J* = 273.6 Hz), 67.6 (CH), 18.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.3 (3F, s); HRMS (EI) Exact mass calcd for $C_{17}H_{15}F_3O$ [M^+]: 292.1070, found: 292.1069.

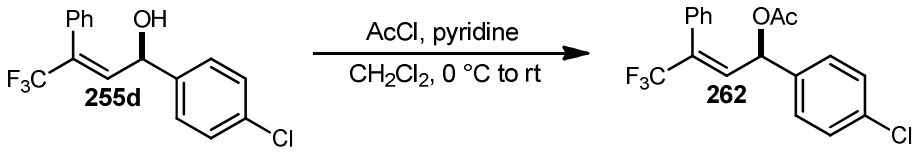
(2*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)but-2-enoic acid (261)[173]



The title compound was isolated from the reaction mixture when **255i** was synthesised as above. To the combined aqueous layers was added 2 M HCl (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (2H, m, Ar**H**), 7.10 (2H, t, *J* = 8.7 Hz, Ar**H**), 6.61 (1H, br, =C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 167.8 (C), 163.5 (C, d, *J* = 249.9 Hz), 143.7 (C, q, *J* = 30.9 Hz), 130.6 (2 x CH, d, *J* = 8.5 Hz), 126.2 (C, d, *J* = 3.5 Hz), 123.5 (CH, q, *J* = 3.4 Hz), 122.1 (C, q, *J* = 275.6 Hz), 115.6 (2 x CH, d, *J* = 22.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.8 (3F, s), –110.9 (1F, s).

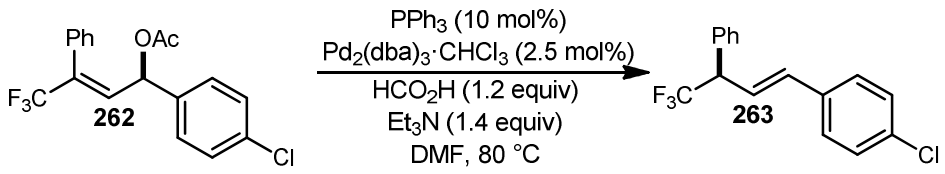
Further Manipulation Reactions

(*R*)-(*E*)-1-(4-chlorophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-yl acetate (262)



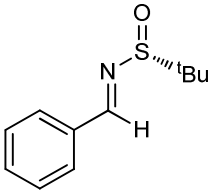
To a solution of **255d** (156 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added acetyl chloride (43 μL, 0.60 mmol) dropwise followed by pyridine (49 μL, 0.60 mmol). The mixture was then warmed to room temperature and stirred for 16 h. The reaction was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the aqueous layer was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave the *acetate ester* **262** as a colourless oil (133 mg, 73%) which was used immediately in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (3H, m, Ar**H**), 7.34-7.31 (2H, m, Ar**H**), 7.24-7.22 (2H, m, Ar**H**), 7.13 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.57 (1H, d, *J* = 8.9 Hz, =C**H**), 6.09 (1H, d, *J* = 8.9 Hz, C**H**OAc), 2.05 (3H, s, C**H**$_3$C=O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.4 (C), 136.6 (C), 134.6 (C), 133.6 (C, q, *J* = 30.6 Hz), 132.8 (CH, q, *J* = 5.5 Hz), 130.8 (C), 129.4 (2 x CH), 129.3 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 122.8 (C, q, *J* = 273.8 Hz), 71.6 (CH), 20.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.0 (3F, s).

(*R*)-1-Chloro-4-[(*E*)-4,4,4-trifluoro-3-phenylbut-1-en-1-yl]benzene (263)



The title compound was prepared following a literature procedure for a similar transformation.[57] To a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (5.2 mg, 0.005 mmol) and PPh_3 (5.2 mg, 0.02 mmol) in DMF (1 mL) at 0 °C was added a solution of the allylic acetate **262** (71 mg, 0.20 mmol) in DMF (0.5 mL) *via* cannula. After stirring at room temperature for 20 min, a solution of HCO_2H (9 μL, 0.24 mmol) and Et_3N (39 μL, 0.28 mmol) in DMF (0.5 mL) was added dropwise and the reaction was then heated at 80 °C for 3.5 h. After cooling to room temperature, saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane) gave the *alkene* **263** (39 mg, 66%) as a colourless oil. $[\alpha]_D^{24}$ +63.6 (*c* 0.22, $CHCl_3$); IR (film) 1491, 1248, 1161, 1105, 1092, 1013, 964, 799, 758, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.36 (5H, m, Ar**H**), 7.33-7.29 (4H, m, Ar**H**), 6.55 (1H, d, *J* = 15.9 Hz, =C**H**Ar), 6.44 (1H, dd, *J* = 15.9, 7.9 Hz, C**H**=CHAr), 4.16 (1H, qd, *J* = 8.8, 7.9 Hz, C**H**CF_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 134.6 (C), 134.5 (C, q, *J* = 1.3 Hz), 134.3 (CH), 133.9 (C), 129.0 (2 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.3 (CH), 127.8 (2 x CH), 126.0 (C, q, *J* = 280.3 Hz), 123.4 (CH, q, *J* = 2.4 Hz), 53.4 (CH, q, *J* = 27.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.0 (3F, s); HRMS (EI) Exact mass calcd for $C_{16}H_{12}F_3Cl$ [M^+]: 296.0574, found: 296.0575. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm); t_r (minor) = 6.2 min; t_r (major) = 7.4 min, 64% ee.

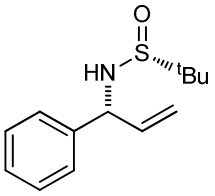
Synthesis of Chiral Sulfoxide Ligand, 257.



(*R*)-2-Methyl-N-[(1*E*)-phenylmethylidene]-propane-2-sulfinamide (265)[174]

The title compound was synthesised according to a literature procedure.[174] To a solution of benzaldehyde (1.70 g, 16 mmol) and ^{t}butanesulfinamide (2.00 g, 16.5 mmol) in dichloromethane (100 mL) was added titanium tetraethoxide (20 mL, 80 mmol). The mixture was stirred at room temperature for 17 hours, then distilled water

(100 mL) was added. The mixture was filtered through celite (~20 g) eluting with dichloromethane (100 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give colourless oil (2.96 g, 88%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (1H, s, **H**C=N), 7.89-7.83 (2H, m, Ar**H**), 7.56-7.45 (3H, m, Ar**H**), 1.27 (9H, s, C**H**$_3$).



(*R*)-2-Methyl-N-[(1*R*)-1-phenylprop-2-en-1-yl]propane-2-sulfinamide (257) [133b)]

The title compound was synthesised according to a literature procedure.[133b)] To vinyl magnesium bromide (1.0 M in THF, 3.8 mL, 3.75 mmol) was added dimethylzinc (1.2 M in toluene, 3.5 mL, 4.25 mmol) and the mixture was stirred at room temperature for 15 minutes. The mixture was then added dropwise to a solution of **265** (523 mg, 2.5 mmol) in THF (15 mL) at −78 °C. After 45 minutes stirring at −78 °C , the reaction was quenched with saturated ammonium chloride solution (30 mL), extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with saturated sodium chloride solution (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/hexane) to give a colourless oil (430 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.36 (4H, m, Ar**H**), 7.33-7.29 (1H, m, Ar**H**), 5.94 (1H, ddd, *J* = 17.3, 10.1, 7.5 Hz, =C**H**), 5.39 (1H, dt, *J* = 17.3, 1.2 Hz, =C**H**), 5.25 (1H, dt, *J* = 10.1, 1.2 Hz, =C**H**), 4.99 (1H, dd, *J* = 7.5, 2.7 Hz, C**H**NH), 2.27 (1H, br, N**H**), 1.26 (9H, s, (C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.5 (CH), 138.3 (CH), 128.9 (2 x CH), 128.1 (CH), 127.2 (2 x CH), 117.5 (CH_2), 61.5 (CH), 55.7 (C), 22.7 (3 x CH_3).

6. References

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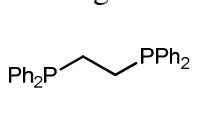
Appendix 1: List of Ligands

Bisphosphine Ligands:



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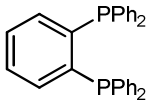
Commercially available



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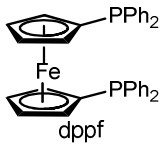
Commercially available



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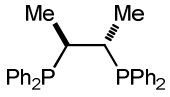

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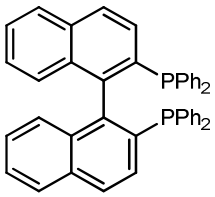

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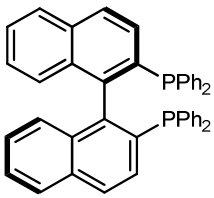
Commercially available



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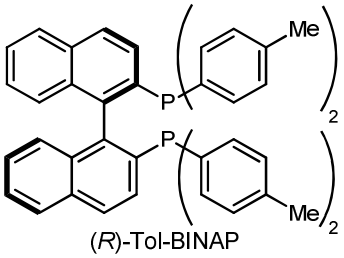

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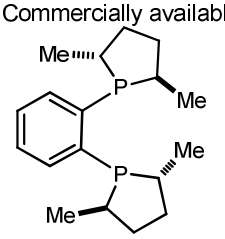

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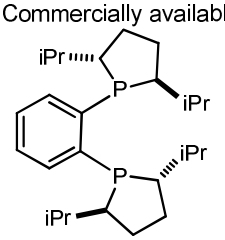
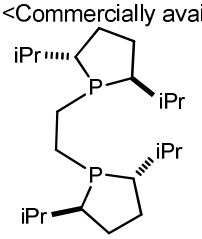
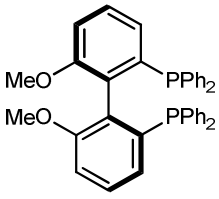


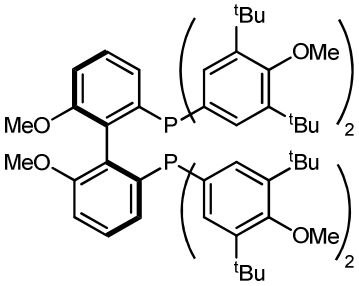
(*S*,*S*)-^{i}PrDuPhos
Commercially available



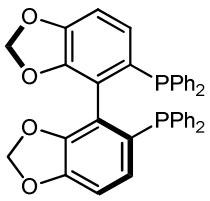
(*S*,*S*)-^{i}Pr-BPE
Commercially available



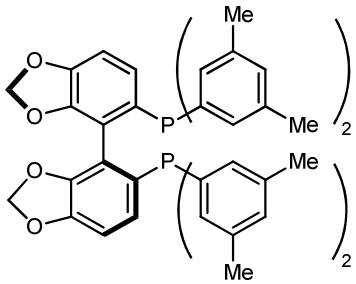
(*S*)-MeO-BIPHEP
Commercially available



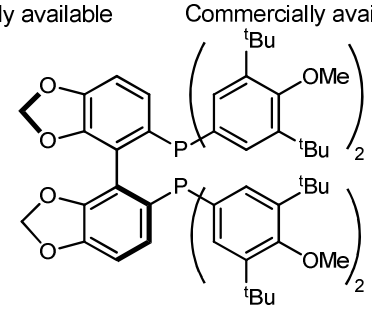
(*S*)-3,5-^{t}Bu,4-MeO-MeOBIPHEP
Commercially available



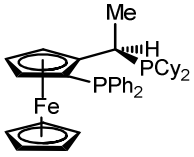
(*S*)-SEGPHOS
Commercially available



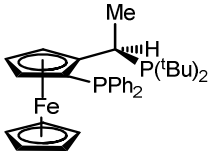
(*S*)-DM-SEGPHOS
Commercially available



(*S*)-DTBM-SEGPHOS
Commercially available

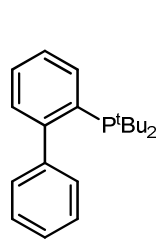


Josiphos, SL-J001-1
Commercially available

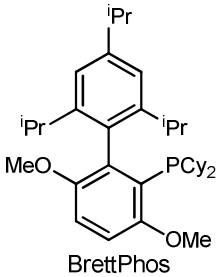


Josiphos, SL-J002-1
Commercially available

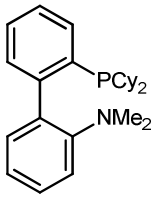
Monophosphine Ligands:



JohnPhos
Commercially available

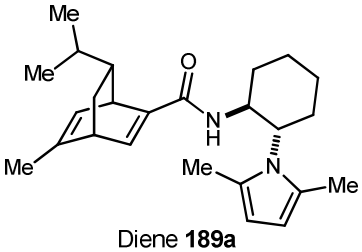


BrettPhos
Commercially available

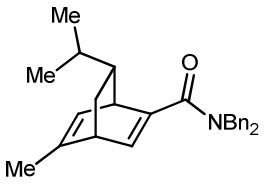


DavePhos
Commercially available

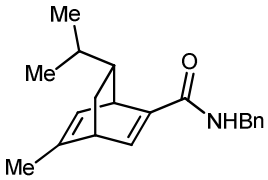
Chiral Diene Ligands:



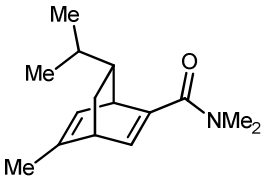
Diene **189a**
Synthesised by Benoit Gourdet[130]



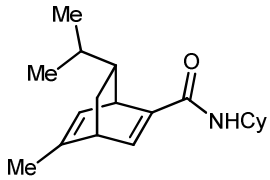
Diene **189b**
Synthesised by Aakarsh Saxena[131]



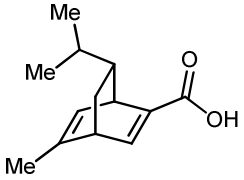
Diene **189c**
Synthesised by Aakarsh Saxena[131]



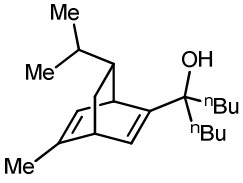
Diene **189d**
Synthesised by Iain Roy[175]



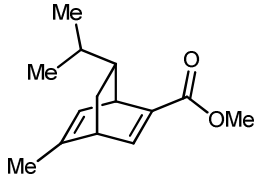
Diene **189e**
Synthesised by Aakarsh Saxena[131]



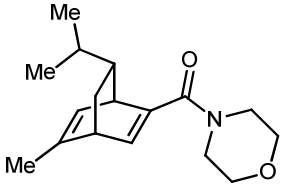
Diene **189f**
Synthesised by Benoit Gourdet[130]



Diene **189g**
Synthesised by Benoit Gourdet[176]

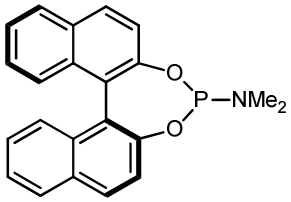


Diene **189h**
Synthesised by Benoit Gourdet[177]

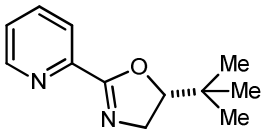


Diene **189i**
Synthesised by Benoit Gourdet[130]

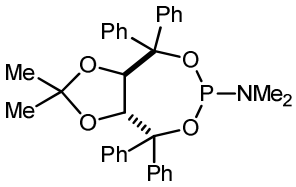
Miscellaneous Ligands:



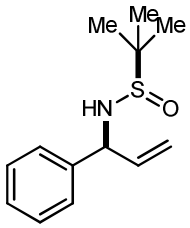
(*S*)-Monophos
Commercially available



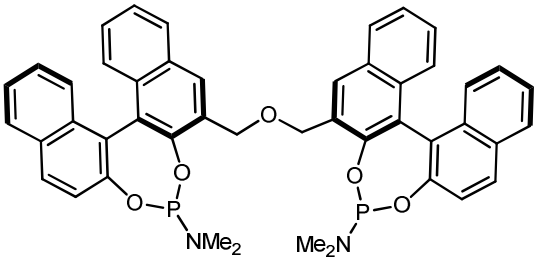
256
Synthesised by Graham Pattison[178]



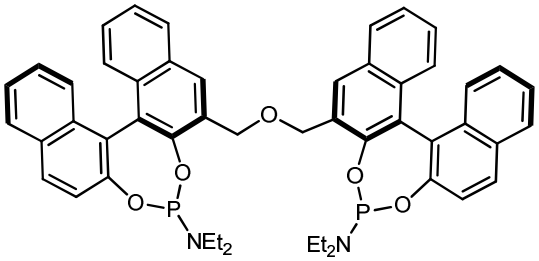
TADDOL-Phosphoramidite
Commercially available



257
See p209 for synthesis



228
See p196 for synthesis



264
See p196 for synthesis